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Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children

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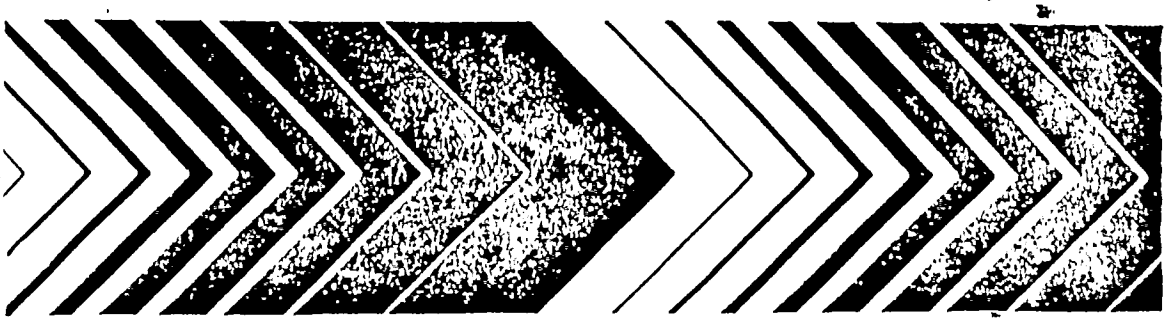

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PREFACE

This assessment of the health effects associated with passive smoking has been prepared by the Human Health Assessment Group, Office of Health and Environmental Assessment, Office of Research and Development, which is responsible for its scientific accuracy and conclusions. The assessment was prepared at the request of the Indoor Air Division, Office of Indoor Air and Atmospheric Programs, Office of Air and Radiation, which defined its scope and provided funding.

The document has been developed under the authority of Title IV of Superfund (The Radon Gas and Indoor Air Quality Research Act of 1986) to provide information and guidance on the potential hazards of indoor air pollutants.

A comprehensive search of the scientific literature for this document is complete through September 1989. In addition, a few studies published since September of 1989 have been included in response to recommendations made by reviewers.

Due to both resource and time constraints, the scope of this review has been limited to an analysis of respiratory effects, with emphasis on the epidemiologic data. Further, because two thorough reviews on passive smoking were completed in 1986 (by the U.S. Surgeon General and the National Research Council), this document provides a summary of those reports with a more comprehensive analysis of the literature appearing subsequent to those reports and an integration of all the results.

With respect to quantitation of lung cancer risk, the document has used the actual epidemiologic data and vital statistics to estimate the number of nonsmokers affected. It does not use high- to low-dose extrapolation models since exposures in the epidemiology studies were at true environmental levels. However, measures of exposure-response and modeling are examined in two appendices. One appendix analyzes the two main, currently-used proxies for environmental tobacco smoke (ETS) exposure, respirable suspended particulates and body cotinine levels. The other appendix examines methodologies and models treating ETS as a complex mixture of carcinogens with both initiating and promoting properties. It also outlines several possible approaches for exposure-response assessment.

Two other issues that have not been addressed in this draft but which have drawn comments from reviewers of earlier drafts are (1) the possible synergistic lung cancer effect of ETS and radon, and (2) the relative lung cancer hazards and risks of home and the workplace. These issues will be more fully covered in a revised version of this document.

It is the Agency's intent to revise and update this document following the public comment period and review by the Agency's Science Advisory Board.

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LIST OF ABBREVIATIONS

ACS	American Cancer Society
ADC	adenocarcinoma
AMW	American war veterans
B[a]P	benzo[a]pyrene
BR	bronchial responsiveness
CEA	cigarette-equivalents approach
C.I.	confidence interval
Coh	cohort study
COPD	chronic obstructive pulmonary disease
CS[1]	current smoker
CSC	cigarette smoke condensate
DA	Direct Approach
ES[1]	ever-smoker
ETS	environmental tobacco smoke
FEF_{25-75}	forced expiratory flow rate, mid-expiratory phase
FEV_1	forced expiratory volume at one second
FS[1]	former smoker
FVC	forced vital capacity
GI	gastro-intestinal
GSD	geometric standard deviation
IARC	International Agency for Research on Cancer
ICRP	International Commission on Radiological Protection
LCD	lung cancer deaths

[1] used for both singular and plural forms

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ABBREVIATIONS (continued)

MAF	marriage aggregation factor
MMAD	mass median aerodynamic diameter
MS	mainstream smoke
NCI	National Cancer Institute
NHIS	National Health Interview Survey
NP	nasopharyngeal
NRC	National Research Council
NS[1]	never-smoker
OR	observed risk
P	pulmonary
PAH	polycyclic aromatic hydrocarbons
PAR	population-attributable risk
RPA	Relative Potency Approach
RR	relative risk
RSP	respirable suspended particulates
RSV	respiratory syncytial virus
SCC	small cell carcinoma
SDA	Seventh-Day Adventists
SS	sidestream smoke
TB	tracheobronchial
U.S. DHHS	U.S. Department of Health and Human Services
U.S. DOT	U.S. Department of Transportation
U.S. SG	U.S. Surgeon General
WHO	World Health Organization

[1] used for both singular and plural forms

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I. EXECUTIVE SUMMARY

In 1986, the National Research Council (NRC) and the U.S. Surgeon General (U.S. SG) assessed the health effects of exposure to environmental tobacco smoke (ETS). Both of the 1986 reports conclude that ETS exposure is causally associated with lung cancer and that children of parents who smoke have increased frequency of respiratory symptoms and acute respiratory illnesses and evidence of reduced lung function. The two reports were developed and edited by different processes, which strengthens the validity of the conclusions common to both reports. The NRC report is the product of a committee of experts; the U.S. SG report is a composite of contributions from individual experts that were edited, based on the review of other knowledgeable individuals, and then cleared through the U.S. Public Health Service.

This document extends the analyses of those reports to include subsequent epidemiologic evidence on the potential association between ETS and (1) lung cancer in nonsmoking adults, and (2) respiratory disease and pulmonary effects in children. It concludes that passive smoking is causally associated with lung cancer in adults and that exposure of young children to ETS from parental smoking, particularly during infancy, is associated with increased prevalence of acute lower-respiratory-tract infections (bronchitis and pneumonia), respiratory symptoms of irritation (cough, sputum, wheeze), and middle ear effusions (a sign of chronic middle ear disease). Passive smoking in early childhood is also associated with reduced lung function in children of mothers who smoke and with a small reduction in the child's rate of pulmonary growth and development. No conclusions are drawn regarding a potential association of parental smoking with the child's increased acute upper-respiratory-tract illnesses (colds and sore throats), an increased prevalence of asthma, or exacerbation of symptoms in asthmatic children.

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This report also estimates that approximately 3800 lung cancer deaths per year among nonsmokers (never-smokers and former smokers) of both sexes are attributable to ETS in the United States. This figure is an extension of the estimate of 1750 (95% C.I. 910, 2660) for female never-smokers alone, an overall value calculated from all the epidemiologic studies on lung cancer and ETS. The 1750 value and its confidence interval includes reasonable estimates of exposure and risk for single female never-smokers. Projection of the 1750 estimate to 3800 for all nonsmokers of both sexes is based on reasonable estimates of exposure and risk for all never-smoking men and for former smokers of both sexes. No further quantitative estimates of ETS-related health effects in adults or children are made.

1.1. ETS AND LUNG CANCER

The U.S. SG (1989) estimates that smoking is responsible for more than one of every six deaths in the United States and that it accounted for 87% of the lung cancer deaths in males and 75% in females in 1985. Smokers, however, are not the only ones exposed to tobacco smoke. The sidestream smoke (SS) emitted from a smoldering cigarette between puffs (the main component of ETS) has been documented to contain many of the same carcinogenic compounds (known and suspected human and animal carcinogens) that have been identified in the mainstream smoke (MS) inhaled by smokers. Exposure concentrations of these carcinogens to passive smokers are variable but much lower than for active smokers. An excess cancer risk from passive smoking, however, is still biologically plausible. (U.S. EPA guidelines [Fed. Reg., 1986] assume that unless there is evidence to the contrary, any level of exposure to a carcinogen carries a potential risk of cancer.)

Based on the firmly established causal relationship of lung cancer with active smoking, the lung is considered to be the site most likely affected by passive smoking. The ubiquity of ETS and its absorption by members of the general population have been well documented by air

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sampling and by bioassays for nicotine and cotinine. This raises the question of whether any direct evidence exists for the relationship between ETS exposure and lung cancer in the general population and what its implications may be for public health. This document addresses that question by reviewing and analyzing the cumulative evidence from epidemiologic studies. These studies compare individuals with higher ETS exposures to those with lower exposures. Typically the study subjects are married women who have never smoked but are married to a smoker (higher exposure) and those married to a nonsmoker (lower exposure). Following the nomenclature of the literature, the higher and lower exposed persons are referred to as "exposed" and "unexposed." Of course there is exposure to ETS from sources other than spousal smoking, collectively designated as "background" exposure, which applies to the so-called unexposed as well as the exposed. Background exposure is taken into account in characterization of population risk (Chapter 4), but it is not required for the statistical assessment of the evidence of excess lung cancer risk from spousal smoking (Chapter 3).

The epidemiologic evidence of a lung cancer hazard is statistically assessed by methods of meta-analysis to obtain overall results. The data and study results included apply to female married never-smokers. Several studies include male subjects, but the percentage of male never-smokers is relatively small and the data are scant by comparison. In some instances former smokers are included with never-smokers. All the ETS exposures are considered to be at true environmental levels.

Based on these analyses and following the U.S. EPA guidelines for carcinogen risk assessment (Fed. Reg., 1986), EPA concludes that environmental tobacco smoke is a Group A (known human) carcinogen. This conclusion is based on a total weight of evidence, principally:

- Biological plausibility. ETS is taken up by the lungs and distributed throughout the body. The similarity of carcinogens identified in SS and MS along with the established causal relationship between lung cancer and smoking make it reasonable to suspect that ETS is also a lung carcinogen.

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- Consistency of response. The two completed cohort studies and sixteen of the 21 case-control studies observed a higher risk of lung cancer among the female never-smokers classified as exposed to ETS. Evaluation of the total study evidence from several perspectives leads to the conclusion that the observed association between ETS exposure and increased lung cancer occurrence is not attributable to chance.

- Upward trend in dose-response. Of the two major cohort studies, the Japanese study (Hirayama) demonstrates a strong association between passive smoking and lung cancer, including an upward trend in dose-response. The upward trend is well supported by the preponderance of evidence in the 13 case-control studies that classified data by exposure level. The Hirayama study has undergone extensive critical review that led to some corrections and revisions but failed to discredit the findings. Differences in life-style and culture may be a factor in the Japanese study reporting a stronger association between ETS and lung cancer than the American study (American Cancer Society).

- Detectable association at environmental exposure levels. Within the population of women who are lifelong nonsmokers, the excess lung cancer risk of those married to a smoker is large enough to be observed. Carcinogenic responses are usually detectable only in high exposure circumstances, such as occupational settings or in highly dosed experimental animals.

- Broad-based evidence. The 21 case-control and three prospective studies provide data from eight different countries and from a wide variety of study designs and protocols conducted by many different research teams. No alternative explanatory variables for the observed association between ETS and lung cancer have been indicated that would be broadly applicable across studies.

- Effects remain after adjustment for potential bias. Current and ex-smokers may be misreported as never-smokers, thus inflating the apparent cancer risk from ETS exposure. The evidence remains statistically conclusive, however, after adjustments for smoker misclassification. The summary estimate of relative risk from raw data of both the case-control and cohort studies is 1.41 (95% C.I. 1.26, 1.57) before adjustment for misclassification and 1.28 (95% C.I. 1.12, 1.45) afterward ($p < 0.01$).

The individual risk of lung cancer from exposure to ETS does not have to be very large to translate into a significant health hazard to the U.S. population because of the large number of smokers and the ubiquity of ETS. Current smokers comprise approximately 30% of the adult U.S. population and consume over one-half trillion cigarettes annually (1.5 packs per day, on average), causing nearly universal exposure to ETS. Cotinine, a metabolite of the tobacco-specific compound nicotine, is detectable in the blood, saliva, and urine of persons recently exposed to tobacco smoke. Cotinine has typically been detected in 50% to 75% of reported

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nonsmokers tested (50% equates to 62 million U.S. nonsmokers of age 18 or above). The estimate of 3800 lung cancer deaths per year in nonsmokers attributable to ETS is based on data from epidemiologic studies at actual environmental exposure levels. Some mathematical modeling is required to adjust for expected bias from self-reported misclassification of smoking status and to account for ETS exposure from sources other than spousal smoking. The approach however, does not rely on a mathematical model of dose-response or low dose extrapolation of observations obtained at extraordinarily high exposure levels.

The components of the 3800 figure include approximately 1750 female never-smokers, 800 male never-smokers, and 1250 former smokers. The 800 value for males is probably low based on information in the limited epidemiologic data for male never-smokers. Little is known about the lung cancer risk of ETS to former smokers. The estimate of 1250 former smokers is based on the assumption that the risk to former smokers is the same as the risk to never-smokers, which may be conservative from a biological perspective. If the estimate of 3800 total lung cancer deaths per year is recalculated using the lower (upper) confidence limit from study data on female never-smokers and the lower (upper) plausible value regarding population exposure to ETS, then a value of 1800 (6100) is obtained. It is unlikely that the number of lung cancer deaths per year attributable to passive smoking by nonsmokers is below 1800 or above 6100.

Other quantitative approaches to characterize population risk could have been used. Dose-response assessments based on the cigarette-equivalents approach to relate the risk of passive smoking to active smoking are reviewed. Published variations of this general approach have typically used either cotinine concentrations or respirable suspended particulates as a surrogate measure of exposure to ETS. They typically ignore the epidemiologic data on ETS and lung cancer and follow the paradigm of low-dose extrapolation from a dose-response curve (a dose-response curve for the lung cancer risk of active smokers in this case). Examples of the cigarette-equivalents approach provide additional estimates of lung cancer risk that, with the

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exception of one low value, range from a few hundred to over 4000 lung cancer deaths per year. Although this report prefers the more direct approach based on epidemiologic data to characterize the lung cancer risk, there are also potential benefits from a dose-response assessment. For example, a dose-response model would be useful for evaluating the effectiveness of abatement procedures and the risk from varied environmental conditions. Methods based on the cigarette-equivalents approach could benefit from improved understanding of the biokinetic similarities and differences between passive and active smoking that may affect extrapolation of risk from active smoking to risk of passive smoking. A mathematical model relevant to that objective is developed as a basis for future study (Appendix C). Three additional quantitative methods for dose-response assessment of passive smoking, along the lines of the general cigarette-equivalents approach, are outlined with solicitation for comments and advice (Appendix D).

1.2 ETS AND RESPIRATORY DISORDERS IN CHILDREN

Exposure to ETS from parental smoking has been previously linked with increased respiratory disorders in children, particularly infants. Several studies have confirmed the exposure and uptake of ETS in children by assaying saliva, serum, or urine for cotinine. A recent study of 433 healthy neonates in central North Carolina found that 64% of them lived in households with a smoker and that 75% of smoking mothers smoked near their infants. Cotinine concentrations were correlated with smoking (especially by the mother) in the infant's presence. Nine to twelve million American children under five years of age may be exposed to cigarette smoke in the home (American Academy of Pediatrics, 1986).

With regard to the respiratory effects of passive smoking in children, this report focuses on the epidemiologic evidence appearing since the two major reports of 1986 (NRC and U.S. SG) that bears on the potential association of parental smoking with detrimental health effects

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in their children. These include symptoms of respiratory irritation (cough, sputum, or wheeze); acute diseases of the lower respiratory tract (pneumonia and bronchitis); indications of chronic middle ear infections (predominantly middle ear effusions); reduced lung function (from forced expiratory volume and flow-rate measurements); prevalence of asthma; exacerbation of symptoms in asthmatics; and acute upper-respiratory-tract infections (colds and sore throats). The thirty or so recently published studies essentially corroborate the previous conclusions of the NRC and U.S. SG regarding respiratory symptoms, respiratory illnesses, and pulmonary function; strengthen support for those conclusions by the additional weight of evidence; and extend research in some directions. In particular, recent studies on middle ear effusion strengthens previous evidence to warrant the conclusion in this report of an association with parental smoking. Additional research also supports the hypothesis that early respiratory illness is associated with long-term pulmonary effects (reduced lung function and possibly increased risk of chronic obstructive lung disease).

The NRC and U.S. SG reports conclude that both the prevalence of respiratory symptoms and the incidence of respiratory infections are higher in the children of smoking parents. Estimates of the increased risk of wheezing vary from zero to over sixfold. In the seven studies of respiratory symptoms subsequent to the two reports, increased cough was observed in a range of ages from birth to mid-teens. Recent studies also supplement the evidence for increased wheeze. Overall, the cumulative evidence supports the previous conclusion of the NRC and U.S. SG. Six of the studies subsequent to those reports have addressed the topic of parental smoking and respiratory illness in children, and all have reported statistically significant results. The cumulative evidence indicates strongly that parental, especially the mother's, smoking is associated with increased incidence of respiratory illnesses in the first one-to-two years of life, particularly for bronchitis and pneumonia. Recent studies also solidify the evidence of a link between parental smoking and increased middle ear disease in young children.

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The U.S. SG and NRC reports both conclude that children of parents who smoke have small decreases in tests of pulmonary output function of both the larger and smaller air passages when compared with the children of nonsmokers. This conclusion is statistically supported, but the topic itself is difficult to study and to evaluate quantitatively because of the relatively large inter-individual variability in temporal patterns of lung growth and development. Family history may be an important factor as well. As noted in the NRC report, if ETS exposure is the cause of the observed decrease in lung function, the effect could be due to the direct action of agents in ETS or an indirect consequence of increased occurrence of acute respiratory illness related to ETS.

Study results on ETS and lung function in children that have appeared since those reports add some additional evidence supporting an association of ETS exposure with decreased lung function. Furthermore, this evidence adds support to the supposition that acute respiratory illness during childhood has a long-term effect on lung growth and development (suggesting an indirect association with ETS exposure, by virtue of its association with increased pneumonia and bronchitis in infants). Overall, the weight of evidence indicates that ETS exposure is associated with decreased lung function in childhood and with a small reduction in their rate of pulmonary growth and development.

This report concludes that the detrimental respiratory effects described in children are associated with exposure to ETS, but a causal association has not been established. Causation is biologically plausible, but other factors that cannot be fully assessed may be influencing the observed study data. One confounding variable, for example, is direct transmission of respiratory infections from smoking parents, who tend to have more infections than nonsmokers. Also, parental recall and the increased incidence of respiratory symptoms in smoking parents may be contributing an upward bias to the response attributable to ETS exposure. Studies have generally not controlled for in utero exposure to agents in tobacco smoke (Chen et al., 1988, is a

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notable exception). Some studies that include children above the age of seven may also be upwardly biased by subjects' unreported experimentation with cigarette smoking.

It is improbable, however, that sources of bias or confounding factors account for the totality of study findings on increased occurrence of detrimental respiratory effects in children of parents who smoke. The overall evidence of a health risk is based on numerous investigations that vary broadly in design and location, source of data, objective, protocol, and methods of analysis. Most studies have controlled for bias and potential confounding factors to the extent possible. The upward dose-response trends exhibited in several studies suggest that an alternative explanatory factor would have to be highly correlated with the level of ETS exposure, e.g., the number of cigarettes smoked per day by the mother. In view of these considerations, the substantial epidemiologic evidence, the serious health consequences of some of the observed effects, and the large number of children potentially at risk, it is prudent and reasonable to treat passive smoking as a risk factor for acute respiratory diseases and chronic obstructive pulmonary disorders in infants and young children.

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2. INTRODUCTION

Over 300,000 deaths per year from all causes of disease in the United States are attributable to cigarette smoking. Some 100,000 of these smoking-related deaths are from lung cancer, which is almost 90% of lung cancer cases from all causes (figures for 1985, U.S. SG, 1989). Forty-three known or suspected carcinogens have been identified in tobacco smoke, most of which are in both mainstream smoke (MS, produced during "puffs") and sidestream smoke (SS, from the cigarette tip between puffs). The relative distribution of carcinogens and other toxins differs between SS and MS, however, often with much larger total amounts (by weight) in the SS from a cigarette. More of the cigarette tobacco is burned in the generation of SS than MS, on average, but a more significant factor is the less complete combustion of tobacco at the lower temperatures producing SS. Environmental tobacco smoke (ETS) to which a passive smoker is exposed principally consists of SS, usually in greatly diluted concentrations depending on the proximity to the source and related environmental conditions, e.g., ventilation. Aging also affects the composition of chemicals in ETS and their relative distribution between the vapor and particulate phases.

Passive and active smokers are exposed to many of the same carcinogens, however, and active smoking has been firmly established as causally related to lung cancer. It is biologically plausible that passive smoking is also causally related to lung cancer. Consequently, the epidemiologic studies available on lung cancer and ETS exposure are examined for detectable evidence of increased lung cancer risk from passive smoking. It should be noted that it is extremely unusual when considering a low dose exposure to an agent known to be carcinogenic at higher doses to have as complete or as extensive a set of measures of exposure to the population at environmental levels; it is almost unprecedented to have epidemiologic evidence in as many different populations as is present for ETS. Nevertheless, statistical analysis of the

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combined study results could be inconclusive. Statistical significance is evidence that an effect is at a sufficiently high level to be detected with the data available; lack of significance only supports the conclusion that it is below a level that the data have adequately high power to detect with assurance.

A first step is to gain some idea of the magnitude of exposure to ETS in the general population. Surrogate measures of ambient concentrations of ETS, such as respirable suspended particulates (RSP), have confirmed passive smokers' exposure in real and simulated environments. Concentrations of cotinine, a tobacco-specific metabolite of nicotine measurable in blood, saliva, and urine, confirm the uptake and systemic distribution of nicotine from ETS in passive smokers. Positive cotinine concentrations in 50% to 75% of self-reported nonsmokers, including persons reporting no exposure to tobacco smoke in the detectable period (up to a few days, depending on the body fluid tested), demonstrate the ubiquity of ETS. Conservatively, over 100 million U.S. adult nonsmokers are exposed to ETS at levels detectable in urinary cotinine assays.

The first epidemiologic results associating passive smoking with lung cancer appeared in the early 1980s. The epidemiologic studies amassed quickly, along with interest in the results and controversy over issues and conclusions. At the request of two Federal Agencies, the U.S. Environmental Protection Agency (Office of Air and Radiation) and the Department of Health and Human Services (Office of Smoking and Health), the National Research Council (NRC) formed a committee on passive smoking to evaluate the methods for assessing exposure to ETS and to review the literature on the health consequences of exposure. The committee's report (NRC, 1986) addresses the issue of lung cancer risk in considerable detail, including summary analyses of the evidence from ten case-control and three cohort (prospective) studies. It concludes that "Considering the evidence as a whole, exposure to ETS increases the incidence of lung cancer in nonsmokers."

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The NRC committee was particularly concerned with potential bias in study results from current and former smokers incorrectly self-reported as lifelong nonsmokers (never-smokers). Under plausible assumptions for misreported smoking habits, it concludes that the true relative risk lies between 1.15 and 1.35, with 1.25 the most likely value. When these relative risks are also corrected for background exposure to ETS to make the risk relative to a baseline of zero ETS exposure, the resultant estimate is 1.42, with a "plausible" range of 1.24 to 1.61. (Technical Note: "Relative risk," RR, is used somewhat generically throughout this report for technical ease and because the name is descriptive of the intended measure. For 2-by-2 contingency tables of raw data from classifying exposed/unexposed against cancer/non-cancer, as analyzed in the NRC report, the sample odds ratio is estimated in place of RR. These terms are discussed in standard texts of statistical methods for epidemiology. A good technical discussion with examples may be found in Agresti, 1990, Section 2.2.)

Two other major reports on passive smoking have appeared: the U.S. Surgeon General's report on the health consequences of passive smoking (U.S. SG, 1986), and the report on methods of analysis and exposure measurement related to passive smoking by the International Agency for Research on Cancer (IARC, 1987). The U.S. SG's report concludes:

> The absence of a threshold for respiratory carcinogenesis in active smoking, the presence of the same carcinogens in mainstream and sidestream smoke, the demonstrated uptake of tobacco smoke constituents by involuntary smokers, and the demonstration of an increased lung cancer risk in some populations with exposures to ETS leads to the conclusion that involuntary smoking is a cause of lung cancer.

The IARC committee emphasized issues related to the physicochemical properties of ETS, the toxicological basis for lung cancer, and methods of assessing and monitoring exposure to ETS. The report quotes the summary statement on passive smoking of a previous IARC working group that found the epidemiologic evidence available at that time (1985) compatible with either the presence or absence of lung cancer risk. Based on other considerations related

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to biological plausibility, however, it concludes that passive smoking gives rise to some risk of cancer. Specifically, the report states:

> Knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during "passive" smoking, and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens, however, leads to the conclusion that passive smoking gives rise to some risk of cancer.

The summary analysis across epidemiologic studies conducted by the NRC is extended in this report to include nine additional case-control studies for which the raw data are available (for 19 from a total of 21 case-control studies). The committee's approach to hazard identification is further complemented by other statistical analysis across studies (meta-analysis) of results adjusted for potential confounding variables. The two major cohort studies (from Japan and the U.S.) are reviewed and compared. Their results are combined with those from the case-control studies to give an overall estimate of relative risk (Chapter 3). The population risk is then characterized by estimation of the annual number of lung cancer deaths among nonsmokers attributable to passive smoking (Chapter 4).

Results from dose-response risk assessments of lung cancer and ETS are examined in this report. The methods tend to be variations on the "cigarette-equivalents" approach, the basis of which is extrapolation of lung cancer risk for passive smoking from a dose-response curve of active smoking. Although this approach makes use of the dose-response information previously obtained for active smoking, the information contained in the epidemiologic studies is not fully utilized. The cigarette-equivalents approach is limited by incomplete knowledge regarding the biological basis for comparing the carcinogenic potential of passive and active smoking. A mathematical model has been developed to aid the study of the biokinetic similarities and differences between passive and active smoking. The model also serves to identify parameters where information is currently lacking.

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The conclusions of this report do not require a dose-response risk assessment, but such a construct could be useful for evaluation of the effectiveness of abatement procedures and for confirmation of population risk estimates from another perspective. Three alternative approaches are described in this report (Appendix D), with solicitation of comments and advice. The three alternatives include: (1) a relative potency approach in which the dose-equivalent potency of ETS relative to a positive control, such as benzo[a]pyrene (B[a]P), is established from animal lung implant studies. That relationship is then included with the relative cancer potency of various polycyclic aromatic hydrocarbons (PAHs) and an existing inhalation dose-response model for B(a)P to establish a dose-response model for ETS; (2) a mixture approach based on a modification of the method in (1) and the relative concentrations of the known lung carcinogens in ETS; and (3) a direct approach using epidemiologic cohort studies on ETS.

Acute health effects in children from household exposure to ETS is a second health-related concern examined in this report (Chapter 5). Epidemiologic evidence subsequent to the major NRC and U.S. SG reports of 1986 is summarized and compared with the conclusions of the two previous reports for respiratory symptoms, respiratory illness, and pulmonary function. Recent studies on related health concerns in children are also reviewed. These studies investigate the effects of parental smoking on prevalence of asthma, chronic middle ear diseases, and upper-respiratory-tract infection, and on the severity of conditions in asthmatics. Potential confounding factors and sources of bias that limit quantitative estimation of health hazards attributable to ETS are addressed.

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3. EPIDEMIOLOGIC EVIDENCE OF LUNG CANCER FROM ENVIRONMENTAL TOBACCO SMOKE

3.1. INTRODUCTION

The 21 case-control studies currently available are listed in Table 3-1. The studies are denoted by the first few letters of the first author's name for easy reference. The NRC report (1986) reviews and analyzes ten of the studies shown in Table 3-1: AKIB, BUFF, CHAN, CORR, GARF, KABA, KOO, LEE, PERS, and TRIC. The study designated as WU in the table is excluded because the raw data were not available. (Raw data consist of the number of exposed and unexposed subjects among lung cancer cases and controls, where a subject is typically classified as exposed to ETS if married to a smoker.) The NRC also excludes an earlier version of the KOO study and the studies by Knoth et al. (1983), Miller (1984), and Sandler et al. (1985) for various reasons (NRC, 1986). Aside from WU, these studies are also omitted from this report.

The U.S. SG's report (1986) contains particularly good summary reviews of the studies available at that time. The studies are selectively described or compared in several sources as well (NRC, 1986; IARC, 1987; Balter et al., 1986; Blot and Fraumeni, 1986; Correa, 1986; Eriksen et al., 1988; Kuller et al., 1986; Repace and Lowrey, 1985; Riboli, 1987; Samet, 1988a,b; Saracci and Riboli, 1989; Weiss, 1986; Wells, 1988b; Uberla, 1987; and Varela, 1987). Appendix A contains summaries of the studies subsequent to the NRC report, two of which are unpublished dissertations (LAMW and VARE). The other studies described in Appendix A include BROW, GAO, GENG, HUMB, INOU, LAMT, SHIM, SVEN, and WU. Tables 3-2, 3-3, and 3-4 display descriptive characteristics of all 21 case-control studies.

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TABLE 3-1. CASE-CONTROL STUDIES OF ETS: CHARACTERISTICS

Study	Location	Matched variables	Final sample matched for ETS	Includes an adjusted statistical analysis[2]
AKIB (Akiba et al., 1986)	Japan (Hiroshima, Nagasaki)	Age, sex, residence, RERF participant	Yes	No
BROW[1] (Brownson et al., 1987)	USA (Colorado)	Age, sex	No[3]	Yes
BUFF (Buffler et al., 1984)	USA (Texas)	Age, sex	No[3]	No
CHAN (Chan and Fung, 1982)	Hong Kong	Matched but variables unspecified	No[3]	No
CORR[1] (Correa et al., 1983)	USA (Louisiana)	Age (± 5), sex, race	No[3]	No
GAO (Gao et al., 1987)	China (Shanghai)	Age (± 5)	No[3]	Yes
GARF (Garfinkel et al., 1985)	USA	Age (± 5)	Yes	Yes
GENG (Geng et al., 1986)	China (Tianjin)	Age (± 2), sex, race, marital status	No[3]	No
HUMB (Humble et al., 1987)	USA (New Mexico)	Age (± 10), sex, ethnicity	No[3]	Yes

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TABLE 3-1. (continued)

Study	Location	Matched variables	Final sample matched for ETS	Includes an adjusted statistical analysis[7]
INOU (Inoue and Hirayama, 1988)	Japan (Kanagawa, Miura)	Age, year of death (± 2.5), district	No[2]	Yes
KABA (Kabat and Wynder, (1984)	USA (New York)	Age (±5), sex, race, hospital	Yes	No
KOO (Koo et al., 1987)	Hong Kong	Age (± 5), residence, housing	No[2]	No
LAMT (Lam et al., 1987)	Hong Kong	Age (±5), residence	No[2]	No
LAMW[8] (Lam, 1985)	Hong Kong	Age, socio-economic status, residence[5]	No[2]	Yes
LEE (Lee et al., 1986)	England	Age, sex, hospital location, time of interview	No[2,4]	Yes
PERS (Pershagen et al., 1987)	Sweden	Age (± 1), sex	Yes	Yes
SHIM (Shimizu et al., 1988)	Japan (Nagoya)	Age (±1), hospital, admission date	Yes	Yes

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TABLE 3-1. (continued)

Study	Location	Matched variables	Final sample matched for ETS	Includes an adjusted statistical analysis[7]
SVEN (Svensson et al., 1988)	Sweden (Stockholm)	Age	No[2]	Yes
TRIC (Trichopoulos et al., 1981)	Greece (Athens)	Age, socio-economic status[4]	No[2]	No
VARE (Varela, 1987)	USA (New York)	Age, sex, county, smoking history	Yes	Yes
WU (Wu et al., 1985)	USA (Los Angeles)	Age (±5), sex, race	No[2]	Yes

[1] Adenocarcinoma only.
[2] Not matched on smoking status (smoker/nonsmoker).
[3] Bronchoalveolar cancer excluded.
[4] Ongoing study modified for passive smoking with follow-up.
[5] "Similar" in age, SES, and residence.
[6] "Similar" in age and SES.
[7] Generally refers to (conditional) logistic regression and to stratification or standardization of variables in analysis.
[8] W.K. Lam is the author of LAMW and co-author of LAMT, a separate study.

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TABLE 3-2. CASE-CONTROL STUDIES OF ETS: CHARACTERISTICS

Study	Percent proxy response[1] Ca	Co	Female[2] age Ca	Co	Source of controls	Number female controls	Percent female controls "exposed"[3]
AKIB	90	88	70.2 35-95	• •	Atomic bomb survivors	270	70
BROW	69	39	66.3	68.2	Cancer cases[4]	47	15[5]
BUFF	82	76	30-79	30-79	Cancer cases[6]	196	84
CHAN	•	•	39-70	39-70	Orthopaedic patients	139	47
CORR	•	•	•	•	Hospital patients[8]	133	46
GAO	0	•	35-69	35-69	General population	375	74
GARF	•	•	≥40	≥40	Cancer cases[9]	402	61
GENG	•	•	≤65	≤65	•	93	44
HUMB	•	•	≤85	≤85	General population	162	56
INOU	100	100	•	•	Cerebro-vascular disease (deaths)	64	•
KABA	•	•	61.6	53.9	Patients[10]	25	60
KOO	•	•	•	•	"Healthy"[11]	136	49

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TABLE 3-2. (continued)

Study	Percent proxy response[1] Ca	Co	Female[2] age Ca	Co	Source of controls	Number female controls	Percent female controls "exposed"[3]
LAMT	•	•	•	•	"Healthy"[12]	335	45
LAMW	•	•	67.5	66	Hospitalized orthopedic patients	144	44
LEE	38[13]	38	35-74	35-74	Patients[14]	66	68
PERS	•[15]	•	•[16]	•	•[17]	347	43
SHIM	•	•	59 35-81	58 35-81	Patients[18]	•	•
SVEN	0	0	66.3		General population	174	66
TRIC	•	•	62.8	62.3	Hospitalized orthopedic patients	190	43
VARE	33[19]	33[19]	67.1[19]	68.1[19]	New York State Dept. of Motor Vehicles	218[19]	•
WU	•	•	<76	<76	Neighbor-hood[13]	52	63

1. "Ca" and "Co" stand for "cases" and "controls", respectively.
2. Single values are the average or median. Paired values are the range.
3. Definition of "exposed" differs between studies. See Table 3-4 and 3-5.
4. Persons with cancers of bone marrow or colon in Colorado Control Cancer Registry.
5. "Exposed" to ETS 4 or more hours/day.
6. Population-based and decedent comparison subjects selected from state and federal records.
7. Assorted ailments.
8. Colo-rectal cancer

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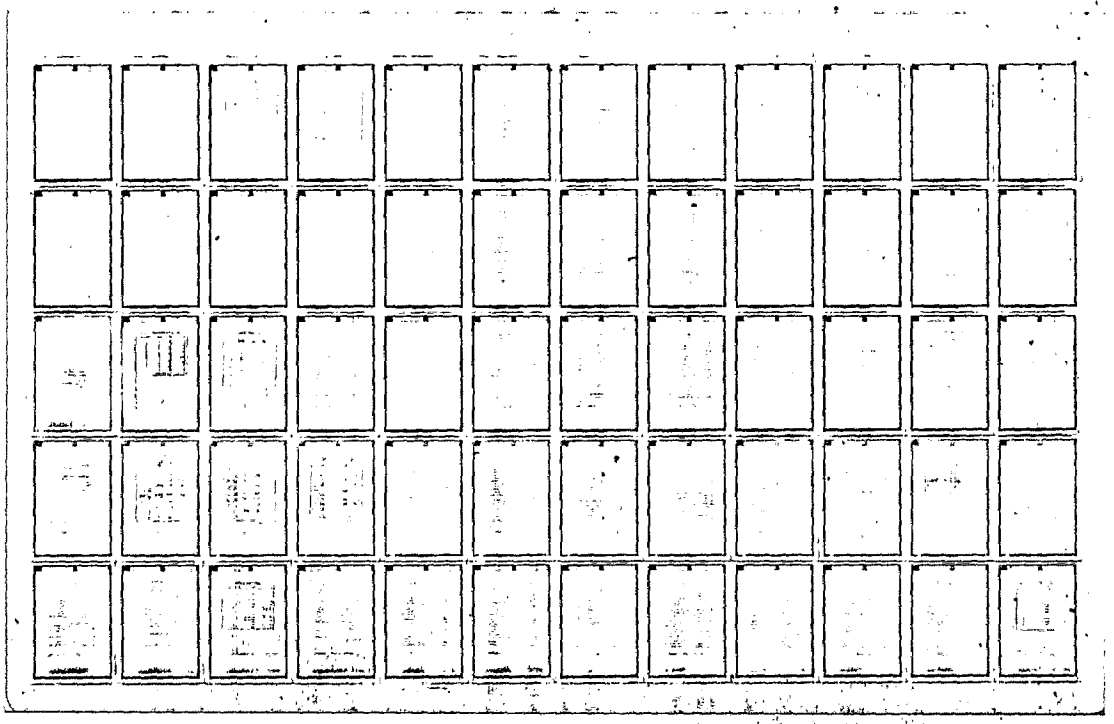

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[10] Diseases not related to smoking.
[11] Selected from a healthy population.
[12] Living in neighborhood of matched case.
[13] Applies only to the 143 patients in the follow-up study.
[14] Excluding lung cancer, chronic bronchitis, ischemic heart disease, and stroke.
[15] No overall percentages given.
[16] Two control groups: 15-65 and 35-85 for both cases and controls in groups 1 and 2 respectively.
[17] Two control groups were randomly chosen from the cohort under study
[18] Patients in the same or adjacent wards with other diseases.
[19] Includes males and females and long-term ex-smokers.
[20] Includes 69 ex-smokers.
• Data not available.

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TABLE 3-3. CASE-CONTROL STUDIES OF ETS: SOURCES

Study	Adulthood: Spouse(s) 1	Adulthood: Spouse(s) >1	Adulthood: Others at home	Adulthood: Away from home	Childhood exposure from mother/father
AKIB	X				X
BROW	X		X	X	
BUFF			X		
CHAN[1]					
CORR		X			X
GAO		X	X	X	X
GARF		X	X	X	X
GENG	X		X[1]	X	
HUMB		X			
INOU	X				
KABA	X		X	X	
KOO	X		X		
LAMT	X				
LAMW	X		X	X	
LEE		X		X[1]	
PERS	X				X
SHIM	X		X	X	
SVEN	X		X	X	X
TRIC		X			

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TABLE 3-3. (continued)

Study	Adulthood: Spouse(s) 1	Adulthood: Spouse(s) >1	Adulthood: Others at home	Adulthood: Away from home	Childhood exposure from mother/father
VARE		X	X	X[4]	
WU		X	X	X	X

[1] Not stated. See footnote 1 of Table 3-4.
[2] Exposure to mother's or father's smoking is presumed to mean in adulthood.
[3] Separate for workplace, travel, leisure.
[4] Separate for workplace and social circumstances.

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TABLE 3-4. CASE-CONTROL STUDIES OF ETS: MEASURE OF EXPOSURE TO ETS AND OTHER SUBSTANCES

Study	ETS exposure measures: Cig./day	Total years	Total cigs.	Other	Related exposures: Cooking/heating	Work/environ.
AKIB	X					
BROW				hrs./day		X
BUFF		X				X
CHAN				X[1]	X	
CORR				pack-yrs.		
GAO		X			X	X
GARF	X[2]			hrs./day		
GENG	X	X				
HUMB	X	X				
INOU	X[3]					
KABA				no units		X
KOO	X	X		X[4]		
LAMT	X[5]					
LAMW				no units		
LEE				X[6]		X
PERS				no units		X
SHIM	X				X	X
SVEN				X[7]		

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TABLE 3-4. (continued)

Study	ETS exposure measures: Cig./day	Total years	Total cigs.	Other	Related exposures: Cooking/heating	Work/environ.
TRIC	X[2]		X			
VARE	X	X	X	person-yrs.		
WU				X[9]	X	X

1 Exposed/unexposed determined from a single question, "Are you exposed to the tobacco smoke of others at home or at work?" (Lam T.H. et al., 1987; Chan and Fung, 1979).
2 Cig./day smoked by husband at home.
3 Smoker at home defined as ≥5 cig./day.
4 Others include total hours of exposure and mean hrs./day.
5 A woman was considered exposed to her husband's smoke if they had lived together continuously for at least one year.
6 Exposure designated as 0 (unexposed), 1,2,3.
7 Exposure is "yes" or "no" for each source.
8 Exposed within the last 5 years.
9 Exposed if husband smoked.

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These studies compare individuals with higher ETS exposures to those with lower exposures. All of them have made observations on never-smoking married women. Those married to a smoker are assumed to be at higher exposures than those not married to a smoker. These two groups are referred to as "exposed" and "unexposed", respectively, following the established terminology. Those terms refer to spousal smoking only, however, and obscure the presence of other sources of ETS, collectively referred to as "background" sources. Background exposure is taken into account in the next chapter, under characterization of the population risk, where it becomes necessary to think of the unexposed classification as referring to exposure from background sources only and the exposed classification as including both background and spousal smoking. For the purpose of hazard identification in this chapter, background exposure does not explicitly enter into the discussion. The relative risk comparison of exposed to unexposed individuals, however, is implicitly a comparison of "exposed to both background and spousal smoke" to "exposed to background only".

Several differences in the case-control studies may be noted. The unit of measure of ETS exposure (e.g., cig./day or total years of exposure) varies between studies. A few studies include former smokers as nonsmokers if they have abstained from tobacco usage for some minimum period, while others do not. Classification of a subject as ETS-exposed depends on the questions asked, which differ across studies. The proportion of controls classified as exposed is shown by study in Figure 3-1. Exposure percentages cover a range from 43% to 84%, a two-fold difference, with the BROW study is an outlier at 15%. The referent populations are defined by a number of parameters, such as whether the subjects were alive or dead and, if alive, whether or not they were hospitalized. Other general study characteristics that vary relate to study design, protocol, interpretation, and analysis of data, potential confounding factors included in the matching and/or data analysis, and confirmation of primary lung cancers. Study differences do not invalidate statistically testing the hypothesis that exposure to ETS is unrelated to lung cancer occurrence. (Technical Note: The Breslow-Day test for homogeneity of the odds ratio is not significant, $p = 0.48$. [Breslow and Day, 1980]) ETS studies have primarily

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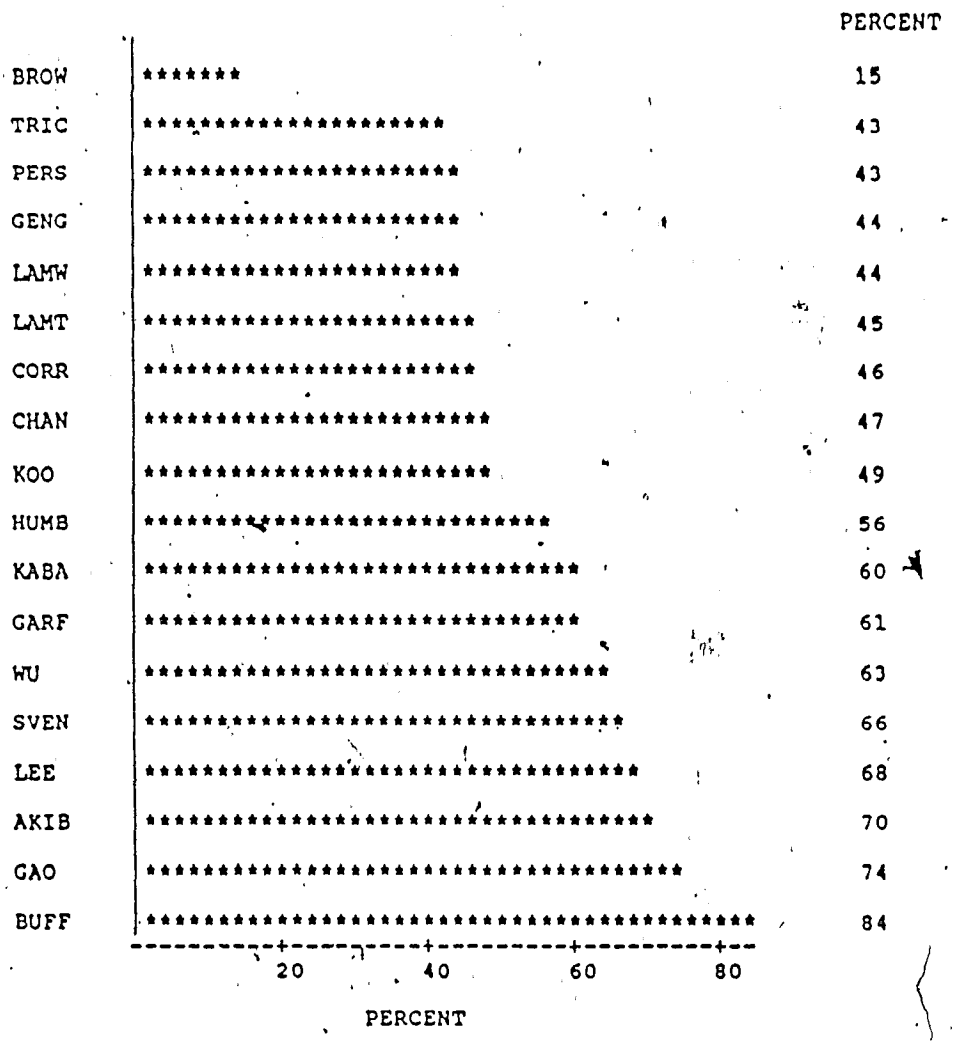

FIGURE 3-1. PERCENTAGE OF CONTROLS EXPOSED TO ETS BY STUDY

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considered exposure to married never-smoking women, generally classified as exposed or unexposed to ETS based on their spouse's smoking status. Consequently, analysis in this report primarily focuses on the data for females. Data on males is sparse by comparison, and there may be sex-related exposure differences to ETS (Cummings et al., 1986; Friedman et al., 1983).

The case-control studies are tested for an association between ETS exposure and lung cancer from three perspectives.

1) Raw data are available for 19 of the 21 studies in Table 3-5. Three statistical tests are applied to these data to test for an association between ETS exposure and lung cancer occurrence.

2) Eleven studies provide results of statistical analyses that adjust for covariables, e.g., age, duration of spousal smoking, etc. Statistical modeling, such as logistic regression, or stratification on variables are two general approaches. The estimated relative risks and confidence intervals from these methods are used in two statistical tests of the combined evidence from the eleven studies.

3) Fourteen case-control studies contain crude classifications of exposure to ETS suitable for evaluating whether there is an upward trend in lung cancer occurrence as ETS exposure increases. These "dose-response" data from the studies are plotted for comparison.

This statistical testing is in the next three sections (Sections 3.2-3.4). It is followed by a discussion of potential sources of bias in the case-control studies (Section 3.5). The two major cohort studies are then described and compared (Sections 3.6 and 3.7), followed by the summary and conclusions of this chapter.

3.2. META-ANALYSIS OF CASE-CONTROL STUDIES FROM RAW DATA

The statistical power to detect a small but meaningful increase in lung cancer risk from a single case-control study is often small, but it can be improved by analyzing the total evidence from all studies simultaneously (meta-analysis). The NRC (1986) followed the lead of a committee member (Wald, 1986) who estimated an overall relative risk across all studies by the statistical method in Yusuf et al. (1985). Blot and Fraumeni (1986) and Wells (1988b) achieved the same objective using the

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TABLE 3-5. CASE-CONTROL STUDIES: "UNEXPOSED" VS. "EXPOSED" FROM RAW DATA

Study	Exposure	No. cases	No. controls	RR[1]	C.I.[1]	S[1]	P[1]$_s$
AKIB							
Female (cig./day)	0	21	82	1.52	(0.88,2.63)	1.48	0.07
	≥1	73	188	1.5	(1.0,2.5)[2]		
Male (cig./day)	0	16	101				
	≥1	3	19	1.8	(0.5,5.6)		
BROW[3]							
Female	unexposed	15	40	1.52	(0.39,5.99)	0.61	0.27
	exposed[4]	4	7	1.5			
Male (hrs./day)	0-3	2	11				
	≥4	2	8	1.38			
BUFF							
Female (tot. yrs.)	unexposed	8	32	0.81	(0.34,1.90)	-0.49	0.69
	exposed[18]	33	164	0.8	(0.3,1.8)		
Male (tot. yrs.)	unexposed	6	34				
	exposed[18]	5	56	0.5	(0.2,1.7)		
CHAN							
Female	unexposed	50	73	0.75	(0.43,1.30)	-1.02	0.85
	exposed[5]	34	66	0.8	(0.4,1.3)		
CORR							
Female[6]	0	8	72	2.07	(0.82,5.25)	1.52	0.06
	≥1	14	61	2.07	(0.8,5.0)		
Male (pack-yrs.)	0	6	154				
	≥1	2	26	2.0			

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TABLE 3-5. (continued)

Study	Exposure	No. cases	No. controls	RR[1]	C.I.[1]	S[1]	P[1]s
GAO							
Female (tot. yrs.)	0-19	57	99	1.19	(0.82,1.73)	0.91	0.18
	≥20	189	276				
GARF							
Female (cig./day)	0	44	157	1.31	(0.87,1.98)	1.29	0.10
	≥1[7]	90	245	1.31	(0.99,1.73)		
GENG							
Female (cig./day)	0	20	52	2.16	(1.08,4.29)	2.19	0.01
	≥1	34	41	2.16	(1.05,4.53)		
HUMB[8]							
Female (cig./day)	0	5	71	2.34	(0.81,6.75)[1]	1.57	0.06
	≥1	15	91	1.8	(0.6,5.4)		
INOU[9]							
Female (cig./day)	<4	4	17	2.55	(0.74,8.78)	1.50	0.07
	≥4	18	30				
KABA							
Female	unexposed	11	10	0.79	(0.25,2.45)	-0.41	0.66
	exposed[10]	13	15				
Male	unexposed	7	7				
	exposed[10]	5	5	1.00	(0.20,4.90)		
KOO							
Female (cig./day)	0	35	70	1.55	(0.90,2.67)	1.56	0.06
	exposed[11]	51	66	1.55	(0.94,3.08)		

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TABLE 3-5. (continued)

Study	Exposure	No. cases	No. controls	RR[1]	C.I.[1]	S[1]	P's
LAMT							
Female (cig./day)	0	84	183	1.65	(1.16,2.35)	2.77	0.003
	≥1	115	152	1.65	(1.16,2.35)		
LAMW							
Female	unexposed	23	80	2.01	(1.09,3.71)	2.24	0.01
	exposed[11]	37	64	2.01			
LEE							
Female	unexposed[12]	10	21	1.03	(0.41,2.55)	0.05	0.48
	exposed[13]	22	45	1.00[14]	(0.37,2.71)[14]		
Male	unexposed[12]	7	16				
	exposed[13]	8	14	1.30	(0.38,4.42)		
PERS							
Female	unexposed[15]	34	197	1.28[14]	(0.76,2.15)	0.91	0.18
	exposed[16]	33	150	1.28[14]	(0.75,2.15)		
SVEN							
Female	unexposed	10	60	1.26	(0.57,2.82)	0.57	0.28
	exposed[16]	24	114				
TRIC							
Female (cig./day)	0	24	109	2.13	(1.19,3.83)	2.55	0.005
	≥1	38	81				
WU[17]							
Female	unexposed	9	22	1.41	(0.54,3.67)	0.70	0.24
	exposed[4]	19	33	1.2			

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Footnotes for Table 3-5.

[1] Values of RR, C.I., S, and P_s on the first row of an entry (boldface) are our calculations for Mantel-Haenszel odds ratio. Values in the second row are from the study. S is the square root of the Mantel-Haenszel statistic with sign of (-) if R<1 and (+) if R>1. P_s is one-tailed significance value from normal tables, and equals one-half the corresponding two-sided p-value for the M-H chi- squared statistic. Confidence intervals are 95% unless noted otherwise.

[2] 90% C.I.

[3] Data communicated from R.C. Brownson.

[4] Exposed if husband smoked.

[5] Exposure based on single question, "Are you exposed to the tobacco smoke of others at home or at work?" (Lam et al., 1987; Chan et al., 1979).

[6] Data partially from Table 12-4, NRC (1986).

[7] Cigar or pipe smoking by husband while at home is included in category of ≥1 cig./day.

[8] Data communicated from C.G. Humble. Eight (total) cases were observed in males, so a separate odds ratio for males alone was not reported in the study.

[9] Raw data were calculated from information given in the reference to INOU by A. Judson Wells.

[10] Based on spouse's current or past smoking habits.

[11] Exposed if husband ever smoked in presence of spouse.

[12] Only the controls in the follow-up study.

[13] Exposed if husband ever smoked during marriage.

[14] Standardized for age.

[15] Data for controls from Saracci and Riboli (1989).

[16] No measure of exposure given.

[17] Raw data were calculated from information in Table 11 of the Surgeon General's report (U.S. SG, 1986, p. 99) by A. Judson Wells.

[18] Any current household member who smokes regularly.

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Mantel-Haenszel (M-H) method (Mantel and Haenszel, 1959; Mantel, 1963), a standard approach for the combination of information from 2-by-2 contingency tables. (Wells included adjusted analyses when available, using the raw data to calculate weights.) The two methods are basically equivalent. In this report, the M-H method is applied to the raw data for females in the case-control studies shown in Table 3-5.

The M-H estimate of relative risk (odds ratio) and its associated confidence interval are shown in boldface type in Table 3-5 for females of each case-control study where the raw data are available (SHIM and VARE are excluded). Each study's own relative risk estimate and confidence interval are also displayed when available. The M-H estimate of the overall RR for females is 1.42 (95% C.I. 1.24, 1.63) for 19 case-control studies. (All confidence intervals hereafter are 95% if not indicated otherwise.) The corresponding value in the NRC report for females of 10 case-control studies and 3 cohort studies is 1.32 (1.16, 1.51). The NRC reports 1.62 (0.99, 2.64) for males. Wells (1988b) obtained an overall relative risk estimate of 1.44 (1.26, 1.66) for females from 14 case-control studies and three cohort studies. Wells' higher estimate may be due in part to his exclusion of the CHAN study, the first and probably least sophisticated of the four Hong Kong studies (CHAN, LAMW, KOO, and LAMT). It also produced the lowest relative risk estimate in Table 3-5, namely 0.75 (0.43, 1.33).

A statistic referred to as "S" is included in Table 3-5. (Technical Note: S is the square-root of the M-H chi-squared statistic with the sign "+" if the odds ratio exceeds 1 and the sign "-" if otherwise. Equivalently, it is the estimated log-odds ratio [ln(RR)] divided by its estimated standard error. The estimator S is approximately normally distributed with mean zero under the null hypothesis that the true relative risk equals one [Woolf, 1955].) The values of P_r in Table 3-5 are the one-tailed significance levels of S for testing the null hypothesis that ETS exposure is unrelated to lung cancer occurrence. The rank ordered values of S are displayed in Figure 3-2.

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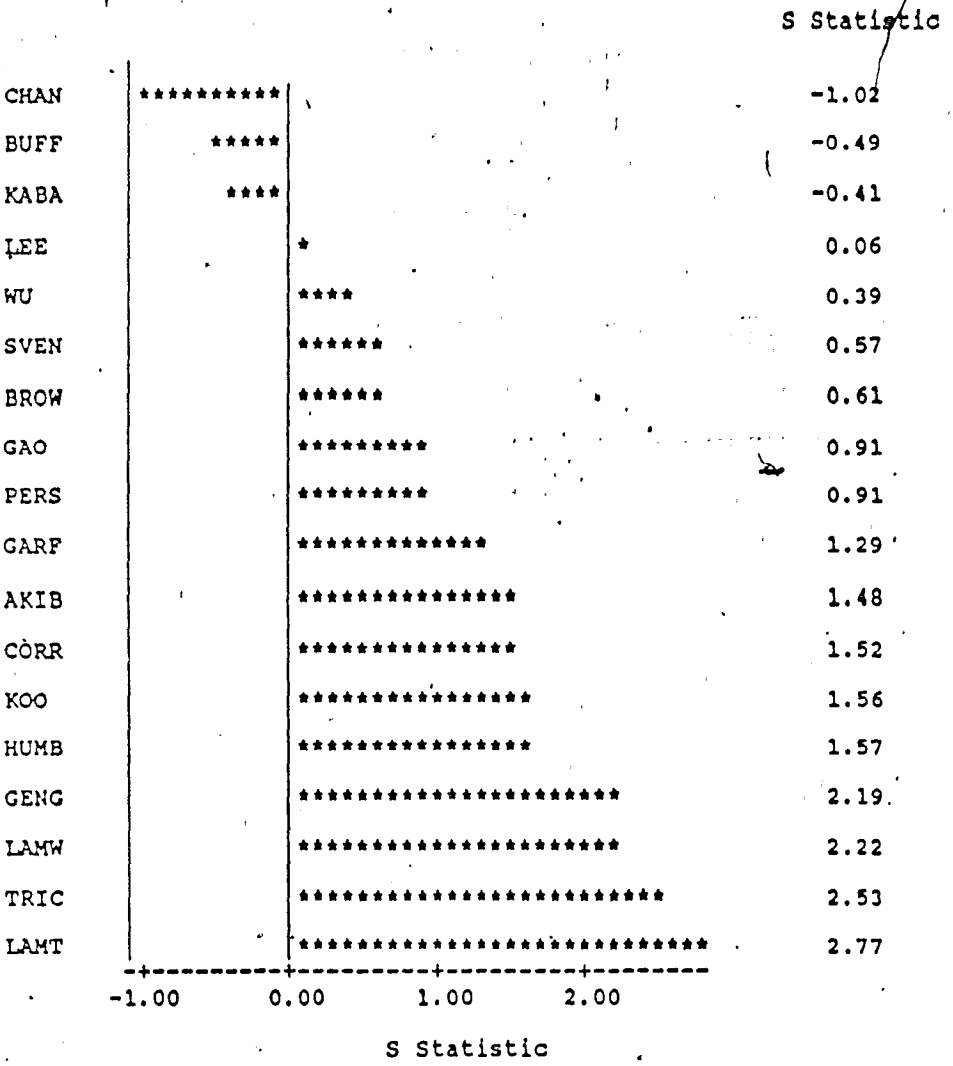

FIGURE 3-2. ORDERED VALUES OF THE S STATISTIC FROM RAW DATA OF STUDIES IN TABLE 3-5

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Three statistical tests are conducted of the null hypothesis. The extended M-H chi-squared test statistic is significant at $p < 0.001$ based on the combined evidence from the raw data shown in Table 3-5. The Wilcoxon sign-ranked test (Hollander and Wolfe, 1973) applied to the values of S in Table 3-5 also is significant at $p < 0.001$. (Technical Note: The signed-rank test requires the test statistic for each study to be symmetrically distributed about zero under the null hypothesis. Since S is approximately normally distributed with mean zero, that assumption is appropriate here.) If the null hypothesis is true, then the four studies with $p_i \leq 0.05$ are making a Type I error (false positive). The chance of that many Type I errors in 19 independent studies is 0.013. The predominance of small values of p_i, in general, is informative. Over half of the 19 p_i values are 0.1 or less, an outcome that would occur with probability less than 0.001 if the null hypothesis is true. All of the tests based on the raw data are statistically significant.

3.3. META-ANALYSIS OF CASE-CONTROL STUDIES THAT INCLUDE AN ADJUSTED STATISTICAL ANALYSIS

An adjusted analysis is generally preferable to an analysis of the raw data, even when the data are matched (Schlesselman, 1982). The two studies for which the raw data are unavailable do include results of an adjusted analysis (SHIM, VARE). Table 3-1 identifies the studies with results adjusted for other variables. Some authors have not included complete details, so the choice of studies for inclusion in this section may be subjective. In eleven reports, the relative risk and confidence interval are given for two or more levels of exposure, e.g., 1 to 20, 21 to 40, or 41+ cig./day smoked by the spouse. The RR and confidence interval at a high exposure in these studies were generally selected for inclusion in Table 3-6, but with some exceptions. For example, the highest exposure category in VARE is so extreme (80+ cig./day) that it contains very little data. In this instance, the response for smoking 20 cig./day as predicted from the

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logistic regression model fitted to all the data is given in Table 3-6. The table entry for GARF is also from an adjusted analysis for a spouse smoking 20 cig./day. Two studies that provide a relative risk without an associated confidence interval (LAMW and SHIM) are displayed in Table 3-6 for completeness, although they cannot be included in the summary analysis.

The RR and confidence intervals in Table 3-6 are the study authors' conclusions that depend on their methods of analysis. To combine the results across studies, the statistic S was calculated from the RR and confidence interval for each study. (Technical Note: It is assumed that ln(RR) is approximately normally distributed. S equals ln(RR) divided by its estimated standard error, as calculated from the confidence interval reported.) The values of S are displayed in Table 3-6 and plotted in Figure 3-3. Five of the studies had significant values of S ($p < 0.05$). The probability of observing five or more Type I errors in 11 independent studies is less than 0.001. Thus, it is highly unlikely that so many significant test results would be observed if there were, in fact, no association between ETS exposure and lung cancer incidence. (Technical Note: No multiple comparison adjustment is necessary because the choice of a single exposure level is made without regard to statistical significance. Test results reported at exposure levels other than the one used are not relevant and no adjustment for multiple comparisons is needed.)

The Wilcoxon signed-rank test was also applied to the S statistics of Table 3-6, as conducted previously with the raw data, to provide another statistical test of the null hypothesis. The outcome is significant ($p = 0.014$). In this test the magnitude of the evidence from each study is a factor. Both statistical tests indicate that the cumulative evidence that lung cancer is related to ETS exposure would be very unlikely to occur by chance alone.

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TABLE 3-6. CASE-CONTROL STUDIES: "UNEXPOSED" VS. "EXPOSED" FEMALES FROM ADJUSTED STATISTICAL ANALYSES

Study	Exposure	RR	95% C.I.	S	P_s
BROW	≤3 vs. ≥4 (hrs./day)	1.68	(0.39,2.97)	1.78	0.04
GAO	0-19 vs. ≥40 (yrs. with smoking husband)	1.7	(1.0,2.9)	1.95	0.03
GARF	0 vs. 20 (cig./day)	1.70	(0.98,2.94)	1.90	0.03
HUMB[6]	0 vs. ≥21 (cig./day)	1.2	(0.26, 5.5)	0.23	0.41
INOU[7]	≤4 vs. ≥ 20(cig./day)	3.09	(1.04,11.81)	1.65	0.05
KOO	0 vs. ≥ 21(cig./day)	1.19	(0.46,3.03)	0.36	0.36
LAMW[2,3]	Exposed by husband	2.64	•	•	•
LEE[2]	Exposed by husband	1.00	(0.37,2.71)	0.00	0.50
PERS[1]	0 vs. ≥ 16(cig./day)	2.40	(0.6,8.7)	1.33	0.09
SHIM[2]	Exposed by husband	1.1	•	•	•
SVEN	Exposed in both childhood and adulthood vs. exposed in neither	1.9	(0.2,3.7)	1.89	0.03
VARE[4]	0 vs. 20 (cig./day)	0.94	(0.76, 1.17)	-0.54	0.70
WU	Exposed by husband	1.2	(0.6,2.5)	0.49	0.31

[1] See footnotes 15-17 of Table 3-2.
[2] Higher RR values associated with adult exposure to smoking by mother or by father's husband. Insufficient information to calculate the S statistic.
[3] No units of exposure. RR = 2.64 with p = 0.02, and RR = 1.61 with p = 0.19, for peripheral and central lung adenocarcinoma, respectively.
[4] From Table 4 of Varela, 1987.
[5] See footnotes 12-14 of Table 3-5.
[6] Discussed in Humble et al. (1987) following Table 4, with 90% confidence interval of (0.3,4.4).
[7] The authors assume that husbands who smoke less than five cig./day do not smoke at home.

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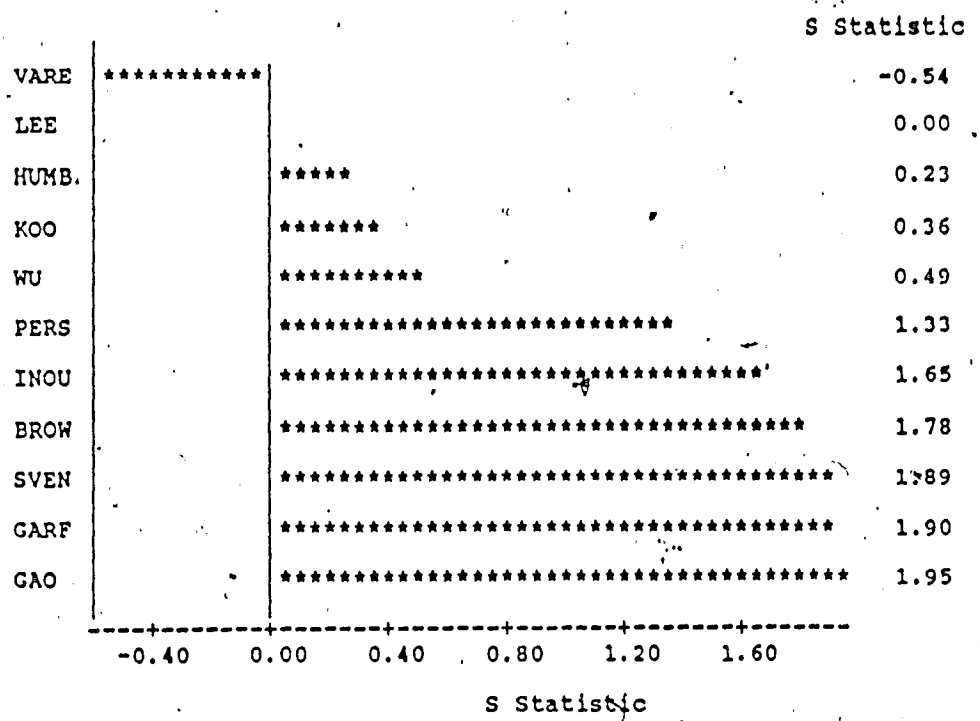

FIGURE 3-3.. ORDERED VALUES OF THE S STATISTIC FROM ADJUSTED ANALYSES OF STUDIES IN TABLE 3-6

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3.4. EVIDENCE OF DOSE-RESPONSE IN CASE-CONTROL STUDIES WITH MORE THAN ONE EXPOSURE LEVEL

Data for studies that report relative risk (RR) by levels of exposure are given in Table 3-7, along with the results of statistical tests for trends when available. The RRs are plotted against exposure and shown in Figure 3-4. Both adjusted and unadjusted estimates of RR are presented, as data permit. Some observations are apparent from the plots. For example, the estimated RRs increase in seven studies: AKIB, CORR, GAO, GENG, INOU, PERS, and TRIC; decrease slightly in one case: LEE; and are variable in the remaining five plots: GARF, HUMB, KOO, LAMT, and VARE.

If RR is independent of ETS, then the predicted RR at the highest exposure level is less than one with probability at least one-half. (Technical Note: If the distribution of the observed RR under the null hypothesis is symmetric, then the value is one-half. The distribution depends on the statistical method used in a study. All appear to be skewed to the right, judging from the confidence intervals. For a right-skewed distribution, the median is less than the mean. Thus, the probability of values greater than one exceeds one-half.) The observed RR at the highest exposure level is less than one in only two of the 13 studies above. The probability of two or fewer such occurrences by chance alone is approximately 0.012. It can be concluded, therefore, that the plots for trend are consistent with conclusions of the previous statistical tests conducted on the case-control studies, i.e., that the observed association between exposure to ETS and increased occurrence of lung cancer deaths is statistically significant.

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TABLE 3-7. CASE-CONTROL STUDIES: EXPOSURE RESPONSE TRENDS FOR FEMALES

Study	Exposure	RR	C.I.[1]	P-Trend	Analysis: Unadjusted	Analysis: Adjusted
AKIB		1.0		0.06	X	
(cig./day)	1-19	1.3	(0.7,2.3)[2]			
	20-29	1.5	(0.8,2.8)[2]			
	≥30	2.1	(0.7,2.5)[2]			
CORR	0	1.0			X	
(pack-yrs.)	1-40	1.18				
	≥41	3.52				
GAO	0-19	1.0				X
(tot.yrs.)[3]	20-29	1.1	(0.7,1.8)			
	30-39	1.3	(0.8,2.1)			
	≥40	1.7	(1.0,2.9)			
GARF	0	1.0		<0.025	X	
(cig./day)	1-9	1.15	(0.8,1.6)			
	10-19	1.08	(0.8,1.5)			
	≥20	2.11	(1.1,4.0)			
GENG	0	1.0			X	
(cig./day)	1-9	1.40	(1.1,1.8)			
	10-19	1.97	(1.4,2.7)			
	≥20	2.76	(1.9,4.1)			
HUMB	0	1.0			X	
	1-20	1.8	(0.6,5.6)[2]			
	≥21	1.2	(0.3,5.2)[2]			
INOU	0-4	1.0		<0.05		X
(cig./day)	5-19	2.58	(0.4,5.7)[2]			
	≥20	3.09	(1.0,11.8)[2]			
KOO	0	1.0				X
(cig./day)[4]	1-10	2.33	(0.9,5.9)			
	11-20	1.74	(0.8,3.8)			
	≥21	1.19	(0.5,3.0)			

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TABLE 3-7. (continued)

Study	Exposure	RR	C.I.[1]	P-Trend	Analysis: Unadjusted	Analysis: Adjusted
LAMT[2]	0	1.0		<0.01	X	
(cig./day)	1-10	2.18	(1.14,4.15)			
	11-20	1.85	(1.19,2.87)			
	≥21	2.07	(1.07,4.03)			
LEE[4]	0	1.0		•		X[4]
	Low	0.92	•			
	High	0,81	•			
PERS[3]	0	1.0		•	X[6]	
(cig./day)	1-15	1.8	(0.6,5.3)			
	≥16	6.4	(1.1,34.7)			
TRIC[5]	0	1.0		•	X	
(cig./day)	1-20	1.95	•			
	≥21	2.55	•			
VARE[10]	0	1.0		•		X
(cig./day)	1-20	0.79	(0.6,1.1)			
	21-40	0.91	(0.6,1.3)			
	41-60	1.23	(0.6,2.4)			
	61-80	0.42	(0.1,2.3)			
	80+	2.86	(0.3, 27.7)			
WU[11]	0	1.0		•		X
(yrs.	1-30	1.2	•			
exposed	≥31	2.0	•			
as adult)						

[1] Confidence intervals are 95% unless noted otherwise.
[2] 90% confidence interval.
[3] Years lived with a smoking husband.
[4] Cig./day smoked by husband.
[5] All histologies.
[6] Exposure at home only. Standardized for age, spouse smoking, and whether currently married.
[7] Small cell carcinoma only. Observed risk was lower for other histologies combined.
[8] Stratified analyses and conditional (logistic) regression produced consistent results.
[9] Data from Trichopoulos et al. (1983).
[10] From Table 2 of Varela (1987) for spouse smoking, presumably including males.
[11] Adenocarcinomas only.

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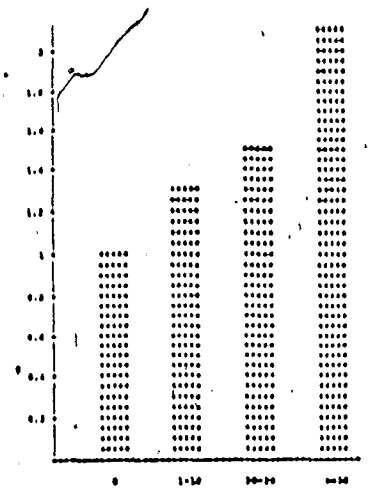
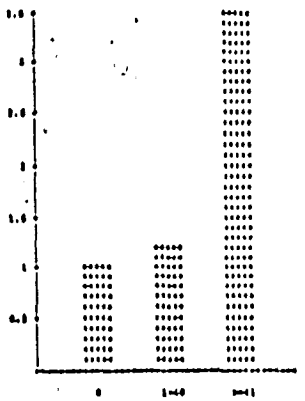
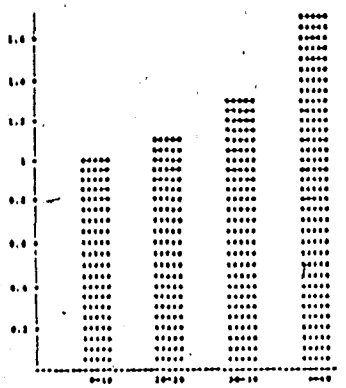


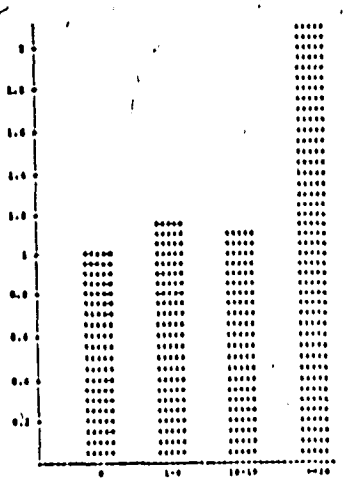
AKIB



CORR



GAO



GARF

FIGURE 3-4. PLOTS OF RELATIVE RISK AGAINST EXPOSURE FOR STUDIES IN TABLE 3-7

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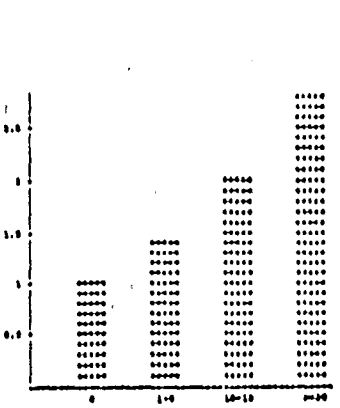
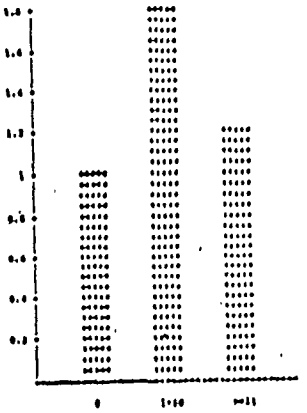


GENG



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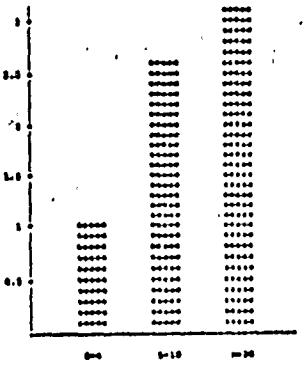
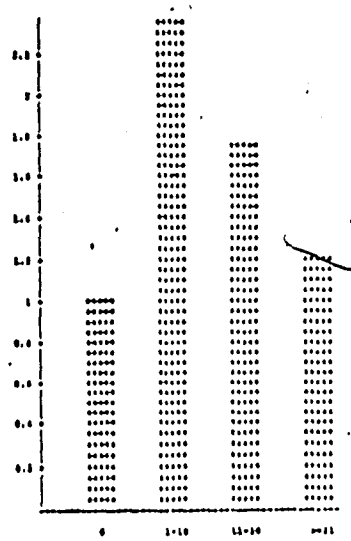


INOU



KOO

FIGURE 3-4. (continued)

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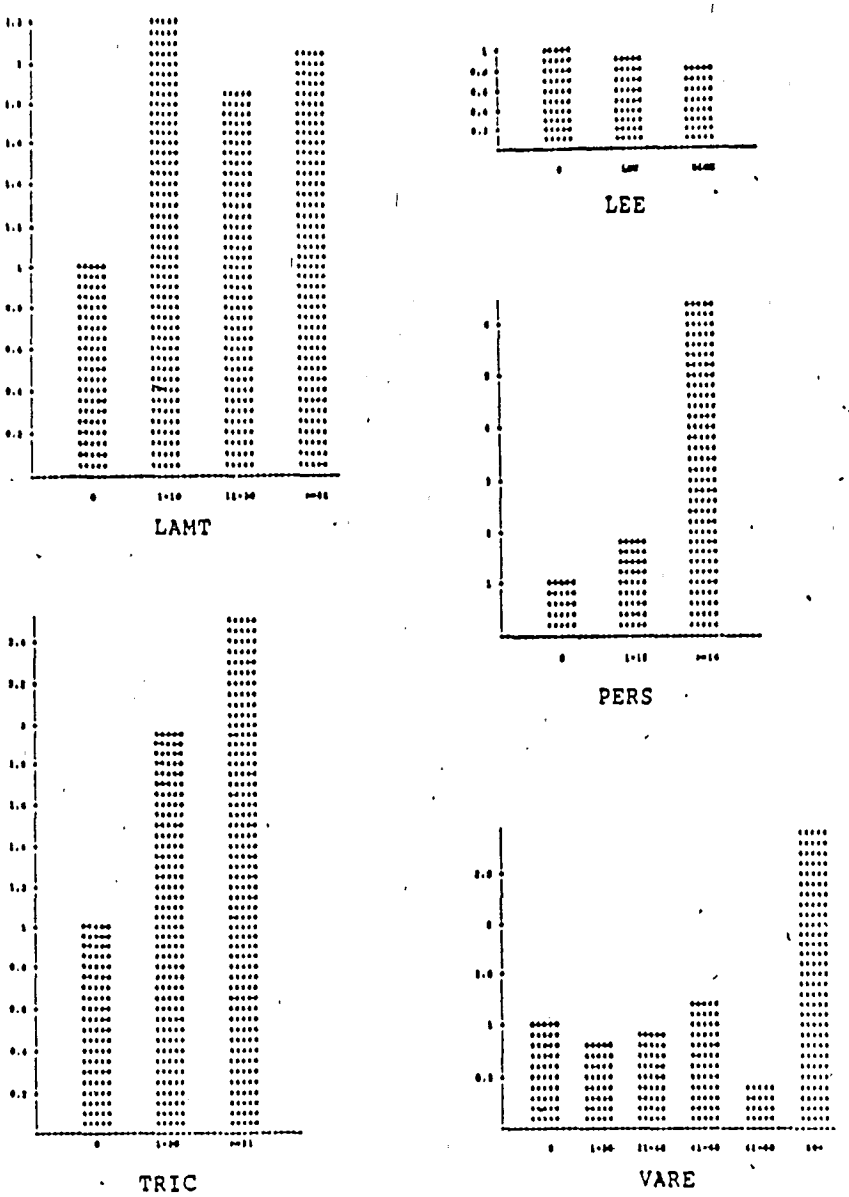

FIGURE 3-4. (continued)

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3.5. BASIC ISSUES IN POTENTIAL BIAS FROM MISCLASSIFICATION IN CASE-CONTROL STUDIES

Bias, particularly misclassification of subjects by smoking status, is not limited to case-control studies. Quantitative adjustment of the overall observed RR for possible misreporting of smoking habits is addressed in detail in Section 4.4.2.

3.5.1. Background

Estimation bias is due to study design, protocol, or method of analysis that apriori makes the expected outcome too large (positive bias) or too small (negative bias). Although sample size and dispersion contribute to outcome variability, neither repeated sampling nor increasing the sample size will affect bias. In either case, the estimate (on average) simply becomes arbitrarily close to the unknown value of interest, i.e., the true RR plus the bias. In practice, each case-control study has its own bias. If bias is largely random over a set of studies, some averaging effect toward zero would be expected. If there is a consistent source of bias in studies, however, sometimes referred to as "systematic bias," then it cannot be expected to disappear as the number of studies increases.

3.5.2. Sources of Bias

Ever-smokers (former and current smokers) are more likely to incorrectly report themselves as never-smokers (NS) than the reverse. A smoker is more likely than a nonsmoker to marry a smoker, so these misclassified ever-smokers (ES) are more likely to be exposed to ETS than true NS. Among lung cancer cases in a study (all of whom are reported NS), those who are actually former smokers (FS) or current smokers (CS) are disproportionately classified as exposed to ETS (assuming that the smoking habit of the spouse is not misreported as well). These cancer cases classified as exposed to ETS may have been at higher risk for lung cancer

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because of a history of smoking, not just because of exposure to ETS. Hence, a lung cancer effect from active smoking may be contaminating the evaluation of the risk of passive smoking. Misreporting among controls tends to overstate the percentage classified as exposed to ETS, due to the concordance of smoking habits in married couples. This artificially elevates the exposed percentage in controls relative to cases, so it contributes to underestimation of risk (or bias in the negative direction).

Subjects classified as unexposed are rarely "truly unexposed"--as supported by data on measurements of cotinine. The NRC report takes this "background" exposure into account in adjusting an overall relative risk for a "net" bias. Recent survey results of Cummings et al. (1989b) provide additional evidence of background exposure in NS. Detectable levels of cotinine were found in 132 of 162 (81%) of the nonsmokers who reported no exposure in the four days preceding the interview. A mean urinary cotinine level of 8.8 ng/mL was found among nonsmokers. Although the study is based on self-selected volunteers, the authors note that the results are consistent with reports from other studies. Cummings and colleagues conclude that exposure to ETS is extremely prevalent, even among those not living with a smoker.

The overall estimate of RR in the NRC report places the excess risk of lung cancer associated with spousal smoking at about 34%. An adjustment for possible misclassification of the never-smoker status reduces the value to 25%. A second adjustment to make the risk relative to a truly unexposed subject, i.e., to take into account a background level of exposure, raises the increased risk to 42%. Consequently, the net adjustment for bias is upwards. The reports of the U.S. SG (1986) and IARC (1987) do not adjust their overall risk estimate for possible bias.

Potential sources of bias have been given considerable attention in the literature, often with an emphasis on the potential for positive bias (over-estimation of relative risk in this case). The following discussion is not complete, but it raises some of the more prominent issues on this

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topic. Many of the potential sources of bias that have been raised in the literature could conceivably create negative bias as well. Of greatest concern, of course, has been the potential for bias from misreported classification of smoking status, i.e., CS or FS reported as NS.

The diagnosis of lung cancer in cases may be a source of bias, e.g., a cancer that originated at another primary site and then metastatised in the lung may be incorrectly diagnosed as a primary cancer of the lung (Samet, 1988b). As an example, Garfinkel et al. (1985) report that about 12% of lung cancer patients identified through hospital records were reclassified after histological review. Some studies addressed this issue by including only pathologically confirmed lung cancers or by considering histological cell type in their analyses (e.g., CORR, GARF, PERS, and others).

Bias due to a proxy respondent in place of the subject has also been raised as an issue by Mantel (1987b) and by Kilpatrick (1987), with evidence from two studies. As reported in Eriksen et al. (1988), respondent bias can be a source of bias in either direction (Sackett, 1979). In general the information provided by surrogates has been comparable to that provided by the individuals themselves (Blot et al., 1985). The recent study by Cummings et al. (1989a) of the passive smoking histories of 380 NS further supports that conclusion. They report substantial agreement between subjects and surrogates on most exposure measures.

Vandenbroucke (1988) and Mantel (1987a) have questioned whether there may be a publication bias, i.e., whether studies with non-significant results are less likely to be published. Vandenbroucke constructed a quantitative approach but found publication bias only for the studies on men. Wells (1988a) reviewed the subject and found it unlikely that publication bias has any substantial effect on the RRs that have been calculated from published reports for passive smoking for either men or women.

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3.6. COHORT STUDIES: BACKGROUND

The three cohort studies that have been conducted are: Garfinkel (1981); Gillis et al. (1984), which was recently updated by Hole et al., (1989); and Hirayama (1981a, 1984); abbreviated as GARF(Coh), GILL(Coh), and HIRA(Coh), respectively. (The "Coh" in parentheses means a cohort study.) The three studies are included in most of the references cited for summary descriptions and comparisons of case-control studies in Section 3.1. The U.S. SG's report (1986) sketches the basic features of the cohort studies and the salient topics of controversy and discussion that appeared in the literature. The Scottish study, GILL(Coh), which observed only a very small number of lung cancer deaths (6 men and 8 women), is included in the risk assessment in the next chapter but is not discussed further in this section.

Unlike the case-control studies, several of which have appeared since the NRC, IARC, and U.S. SG reports of 1986 and 1987, the two major cohort studies, GARF(Coh) and HIRA(Coh), first appeared in 1981. Consequently, most of the issues regarding these two studies and their somewhat dissimilar results surfaced well before the three major reports were prepared. Critical scrutiny of the Hirayama study had already appeared and had been adequately addressed by Hirayama, as described in the U.S. SG and NRC reports. Judging from the roundtable discussion at the symposium "Medical Perspectives on Passive Smoking" (Lehnert, 1984), previous challenges to Hirayama's work regarding data analysis and other issues appear to have been resolved, aside perhaps from the issue of misreported smoking habits. Even one of the strongest critics of epidemiologic findings (P.N. Lee) offered a qualified acceptance of the strength of the statistical evidence in the Hirayama study: "It is ... clear in Dr. Hirayama's data that if one takes the age of the husband or wife into account and does the analysis correctly, there is a statistically significant association in lung cancer risk, but the significance is not nearly as marked as in the incorrect analysis."

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In contrast, the study by Garfinkel and colleagues at the American Cancer Society (ACS) has undergone much less questioning and critical examination, although the problems experienced in conducting the study and the potential for error in the results have not gone unnoticed. The difference in outcomes in HIRA(Coh) and GARF(Coh) has been a source of concern to many, but to our knowledge, no one has conducted a statistical review of GARF(Coh) or compared the statistical methodology in the two studies. Those topics are addressed in the following section.

3.7. SOME COMPARATIVE ASPECTS OF THE TWO MAJOR COHORT STUDIES: HIRA(Coh) AND GARF(Coh)

3.7.1. Overview

An increase in risk of lung cancer from ETS was observed in both cohort studies, with statistical significance ($p < 0.05$) achieved in HIRA(Coh) but not in GARF(Coh). In the former study, the observed risk increases as spousal smoking increases (a "dose-response" relationship that would be expected if passive smoking is causally related to lung cancer). Data from the American study, however, estimate a higher risk at the lower of two exposure categories (spouse smokes < 20 cig./day) than at the higher one (spouse smokes 20+ cig./day). Some researchers have interpreted this outcome as evidence that there is not a "dose-response" relationship in the American study, or more strongly, that the results demonstrate that there is no increased risk of lung cancer from ETS exposure. The statistical evidence supporting an association between lung cancer incidence and ETS exposure in GARF(coh) is inconclusive--it is consistent with either the presence or absence of a true dose-response relationship. This conclusion follows from the 95% confidence intervals for the lung cancer mortality ratio at the low (< 20 cig./day) and high (20+ cig./day) exposures, equal to (0.85, 1.89) and (0.77, 1.61), respectively. These confidence intervals are consistent with a wide range of possibilities. For example, 1.0

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(corresponding to no increase in lung cancer mortality) is in both confidence intervals, but so are values corresponding to a substantial dose-response relationship, e.g., 1.25 and 1.50 at the low and high exposures, respectively.

In the following section, the Japanese study (HIRA(Coh)) and the American study (GARF(Coh)) are reviewed, with an emphasis on the cultural differences in the populations sampled and the differences in study design, execution, and analysis of data that may help to compare outcomes of the two studies. In the final section, data comparisons are made for the two studies to evaluate if there are widespread differences across all age-exposure group combinations, or just specific ones.

3.7.2. Comparative Review and Discussion of the Cohort Studies

HIRA(Coh) is a census-population based study of adults aged 40 or above, begun in 1965 in 29 Health Center Districts in Japan. A total of 200 cases of lung cancer occurred among the 91,540 nonsmoking married women who were followed. A total of 265,118 subjects were enrolled for the entire study (122,261 males and 142,857 females, including unmarried women) accounting for 94.8% of the total census in the study area. Subjects were tracked by establishing a record linkage system between the data/interview records and death certificates (Hirayama, 1983b, 1984). Interviewers were blind to the smoking status of subjects (NRC, 1986).

In the Japanese study, relative risks of 1.42, 1.58, and 1.91 were observed for nonsmoking wives with husbands who smoked 1 to 14, 15 to 19, and 20+ cigarettes per day, respectively. The corresponding value for women whose husbands were former smokers is 1.36, which falls between the values for nonsmoking and light smoking husbands (Hirayama, 1984). The observed increase in risk across the exposure categories, with former smokers classified between nonsmokers and the 1 to 14 cig./day group, is statistically significant by the Mantel-Haenszel test (one-tailed $p < 0.002$). Also, RR for women married to smokers increased with age and

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with duration of exposure to spousal smoking (age and duration of exposure are likely correlated, so these should not be construed to be independent results).

GARF(Coh), the ACS's Cancer Prevention Study (CPS-I), began in 1959 when 68,000 volunteers in 25 states enrolled more than one million men and women for long-term follow-up Volunteers were instructed to recruit people they knew well. Subject participation was fairly evenly divided across large cities, small cities and suburbs, small towns, and rural areas. Overall, about 3% of the population over the age of 45 in 1121 counties was recruited. Enrollment included all family members of age 30 or above, provided at least one member of the household was at least 45.

Each year, for six years, the volunteers were asked to report the vital status (alive or dead) of the persons contacted. For subjects who had died, death certificates were obtained from state departments of health to determine the cause of death. Additionally, physicians who certified the cancer deaths were contacted and asked to supply information to verify the primary sites of the cancers. In the first six years, information was received confirming the primary sites of cancer in 78% of the cases, and microscopic confirmation was obtained in 69% of the cases. Death certificates overstated the lung cancer rates by 11.8% (Garfinkel, 1981, 1984, 1985). The study was essentially terminated after six years, as originally planned in 1965, until it was decided to conduct a second follow-up beginning in 1971. Follow-up was achieved for 98.4% of the subjects. The follow-up was terminated, however, because tracing became increasingly difficult due to death or movement of the volunteers and their substitutes (Garfinkel, 1985). Apparently death certificates did not continue to be followed up by a medical report after the first six years. For lung cancer cases in all women, married or not, 203 out of a total of 564 (36%) reported by death certificates were accompanied by a medical report.

The American study does not provide conclusive results regarding a possible association of lung cancer with ETS exposure. The ratio of observed to expected lung cancer deaths, referred

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to as the mortality ratio (Garfinkel, 1981), is 1.27 and 1.10 for nonsmoking women with husbands who smoked < 20 cig./day and 20+ cig./day, respectively. Neither value is statistically significant. When data from the Hirayama study are grouped according to the same exposure levels (< 20 cig./day and 20+ cig./day), the observed relative risks are 1.45 and 1.91, with one-tailed p-values of 0.03 and 0.001, respectively (Hirayama, 1984).

The American cohort study appears to contain more statistical uncertainty than the Japanese study. Some of the general factors contributing to uncertainty in study data are related to sample size, variability in the population sampled, sample design and protocol, treatment of missing or incomplete data, accuracy and reliability of collecting and reporting data, and methods of statistical analysis. When the data produce a clear pattern, such as HIRA(Coh), with a consistent upward trend across exposure categories and age groups that cannot be ascribed to chance alone, one has some assurance that the sources of variability are not obscuring a dose-response relationship. Apparent differences between outcomes of the two studies could be due to one or more sources: (1) a real difference in risk in the populations studied (perhaps due to higher exposure or uptake of ETS); (2) differences in the way the studies were designed, conducted, or interpreted; or (3) chance occurrence alone. There is suggestive evidence for the first two alternatives. Subjects in the American study were followed for 12 years compared to 16 years in the Japanese study (Hirayama, 1984), so the proportion of subjects with lung cancer would be expected to be lower in the American study. As reviewed in the U.S. SG's report (1986), the relatively high risks observed for nonsmokers whose husbands smoked led to speculation that Japanese women may report themselves as nonsmokers when they actually smoke (also see Lehnert, 1984). However, some reassurance of the validity of self-reported information from Japanese women is provided by the AKIB study, which found strong concordance between self-reported smoking status and the reports from the next-of-kin.

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Hirayama has emphasized the importance of properly defining passive smoking. He classifies direct passive smoking as exposure from within approximately 1 to 1.5 meters of the source and indirect passive smoking as exposure from a greater distance (Hirayama, 1984; Lehnert, 1984). Direct passive smoking is of much greater concern than indirect passive smoking (Lehnert, 1984). Japanese wives may experience more direct passive smoking if they tend to be in closer proximity to their smoking husbands than American wives. Related factors that may contribute to a net increase in exposure for Japanese wives relative to their American counterparts include house sizes, the number of smokers per volume of air, proximity of nonsmoking spouse's sleeping area to spouse's smoking area, and the amount of time a nonsmoking spouse is in the home. Hirayama (1981b) notes additional differences between Japan and America that may influence exposure, such as a higher percentage of office workers among females in the United States than in Japan and a higher divorce rate in the United States. Japanese wives may be much less exposed to ETS from sources other than spousal smoking in the home than U.S. wives, i.e., background exposure to ETS may be lower for Japanese wives. (Technical Note: An increase in exposure to household ETS and a decrease in exposure from other sources for Japanese women relative to U.S. women would both contribute toward a higher RR for the Japanese if passive smoking is causally related to lung cancer.) Two additional factors that may affect a comparison between the United States and Japan include total cigarette consumption and lung cancer rates due to causes not related to tobacco smoke.

These differences between the U.S. and Japan weigh heavily in favor of Japan as the more fertile sociological environment for observing an excess risk of lung cancer from passive smoking by means of an epidemiologic study based on spousal smoking. Exposure to household ETS appears to be higher in general, with more direct passive smoking, and exposure from other sources (background exposure) appears to be lower. These factors contribute to a larger relative exposure to ETS between the so-called exposed and unexposed groups. If passive smoking is a

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risk factor for lung cancer, then the observed relative risk should be higher when the relative exposure to ETS between the comparison groups is higher (mitigating factors not withstanding). There are also some differences in the methods of analyzing and interpreting data in the two cohort studies, as described in the next section.

3.7.3. Comparative Data Analysis of the Cohort Studies

The measures of risk reported in HIRA(Coh) and GARF(Coh), the odds ratio and the mortality ratio, respectively, are not identical statistics. Neither are the statistical methods to control for age the same. The method applied by Hirayama (Hirayama, 1984) is the Mantel-Haenszel procedure, commonly used to standardize for age and other factors that may have an influence. To control for age by this method, for example, study observations are grouped by time intervals. Comparisons between exposure groups are made at each time interval, and then the results are combined across intervals to test for a difference between exposure groups (the extended M-H procedure). The method of analysis used by Garfinkel (1981) is somewhat different (described more fully in Hammond et al., 1975, 1976). Adjustment for age is handled by assigning weights according to person-years with a smoking husband. The results are analyzed as quantal response data.

The method previously applied to non-ETS data in the American study is used to statistically adjust for potential confounding variables (Hammond et al., 1975, 1976). Groups are formed from the data matched on age, race, highest educational status of the husband or wife, residence, and whether or not the husband is occupationally exposed to dust, fumes, or vapor (Garfinkel, 1981). The ratios of the number of adjusted lung cancer deaths in the low (< 20 cig./day) and high (20+ cig./day) exposure categories to the corresponding number in the control group, i.e., the nonsmoking women with nonsmoking husbands, are reported to be 1.37 and 1.04, respectively, neither of which is statistically significant. Using data from the American

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study that includes age at time of death, duration on study, and whether death was due to lung cancer or another cause (supplied by L. Garfinkel), the Mantel-Haenszel method was applied controlling for age and duration on study. Controlling for these two factors simultaneously, however, did not produce statistical significance or otherwise alter previous conclusions.

For further comparison, the descriptive data from GARF(Coh) corresponding to the age groups and exposure classifications of data published for HIRA(Coh) (Hirayama, 1984, Table 1) were placed side-by-side for visual comparison (Table 3-8). Relative to the general pattern of response in the Japanese study, the American data appear to be at greatest variance from what might be expected in the two subgroups at highest exposure (20+ cig./day) in the age classifications 40 to 49 and 50 to 59. Further review of those data for completeness, possible sources of bias, or unanticipated anomalies may be illuminating.

3.8. SUMMARY AND CONCLUSIONS

The primary focus of this chapter has been on hazard identification, in this case a statistical assessment of the combined evidence from 21 case-control studies and three cohort studies of an association between ETS exposure of never-smoking women and lung cancer. The case-control studies vary with regard to inclusion of raw study data, an adjusted statistical analysis (adjusting, or controlling, for covariables in the statistical analysis), and dose-response information to test for upward trend (lung cancer occurrence reported by the amount spouse smokes).. The statistical assessment was conducted from these three perspectives. Overall, analysis of unadjusted odds ratios (19 studies) indicated a significant lung cancer relationship ($p \leq 0.001$ for both statistical tests used. The two statistical tests based on authors' adjusted statistical procedures in 11 studies were also significant ($p \leq 0.001$ and $p = 0.014$). To check for an upward trend in response, observed relative risk was plotted against exposure (e.g., number of cig./day smoked by the husband) for the 13 case-control studies reporting these data.

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TABLE 3-8. TWO COHORT STUDIES: FEMALE LUNG CANCER DATA FOR SIMILAR AGE AND EXPOSURE GROUPS[1]

Age[3]	Study[4]	Husband's smoking habit[2]		
		Nonsmoker	1-19	20+
40-49	G	9/23,743 (3.8)	6/11,791 (5.1)	12/26,918 (4.5)
	H	4/6,229 (6.4)	14/13,779 (10.2)	16/10,764 (14.9)
50-59	G	31/25,108 (12.3)	25/13,528 (18.4)	21/24,184 (8.7)
	H	10/7,791 (12.8)	28/13,720 (20.4)	24/9,820 (24.4)
60-69	G	23/15,138 (15.2)	16/6,884 (23.2)	20/7,299 (27.4)
	H	18/7,120 (25.3)	37/9,756 (37.9)	23/4,651 (49.4)

[1] Entries are (number of lung cancer deaths)/(number at risk), stated as a percentage (× 100) in parentheses. Data for age 70-79 are omitted because of small sample sizes and small number of lung cancers observed. Data for "G" were supplied by L. Garfinkel. Data for "H" are in Hirayama (1984).

[2] Cigarettes/day.

[3] Women's age for G; Husband's age for H.

[4] G:GARF(Coh) H: HIRA(Coh).

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Although outcomes vary, an upward trend was observed in more instances than could be attributed to chance alone. Tabled study characteristics did not suggest common features among the studies that might explain their findings. The statistical results solidly support the conclusion that the observed association between lung cancer and ETS exposure in case-control studies is not attributable to chance occurrence.

The cohort studies were addressed separately from the case-control studies for several reasons. The size of the two major studies, the U.S. study by the American Cancer Society and the Japanese study by Hirayama, might dominate the outcome of some comparisons with case-control studies. Also, the cohort studies differ from the case-control studies in design, execution, and numerous other characteristics. The Japanese cohort study alone provides compelling evidence of a lung cancer risk associated with ETS exposure. Although some corrections to the initial calculations were required, it has withstood extensive critical examination since its appearance in 1981 (see NRC, 1986). Results of the American cohort study are less conclusive. Differences in culture and life-style between the U.S. and Japan suggest that ETS exposure from spousal smoking may be higher, and exposure from background sources lower in the U.S. than in Japan. In view of other study evidence of an upward trend in response, the more pronounced outcome observed in the Japanese study might be anticipated.

Although the American cohort study weakly indicates an increased lung cancer risk from ETS exposure, the data have an observed inversion in dose-response, i.e., lower response at high exposure to spousal smoking than at moderate exposure. Further study of the data to see if the inversion can be explained may be warranted, especially since this study is the largest in the U.S. and is the only U.S. cohort study. A statistical analysis of the data adjusted for survival was not helpful. Consequently, the well-patterned response of lung cancer occurrence by subjects' age and husband's smoking status in the Japanese experience were used as a model to illuminate departures in the American survey. Data in the American study deviate most from what might

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be expected in the two subgroups at highest exposure (over 20 cig./day) in age groups 40 to 49 and 50 to 59. Further examination of this subset of the data may be warranted.

Based on the statistical results of this chapter, this report concludes that passive smoking is associated with an increased risk of lung cancer. The stronger conclusion of a causal association, however, is not warranted from these statistical tests alone. Other factors must be considered as well, including the likelihood that the observed association is attributable to systematic bias or the presence of a confounding variable. Further analysis relevant to whether the stronger conclusion of causal association is relevant is given in the next chapter.

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4. ASSESSMENT OF LUNG CANCER RISK FROM ETS

4.1. INTRODUCTION

The preceding chapter addressed the topic of hazard identification and concluded that ETS exposure is associated with lung cancer. Statistical tests alone, however, do not generally warrant the conclusion that two variables are causally related, i.e., that one of the variables is a contributing cause of the other. The total weight of evidence needs to be considered. In particular, the likelihood that the observed association is attributable to a confounding variable or a systematic source of bias needs to be considered. If it is concluded that ETS is causally associated with lung cancer, then the next step is to characterize the magnitude of the population risk.

Review and analyses of the epidemiologic studies described in Chapter 3 and supplemented by Appendix A have not indicated a correlate of ETS that may explain the observed association between ETS and lung cancer. Among the potential sources of bias discussed, however, misclassification of smoker status needs to be examined as a possible explanation of the observed effect. Its significance is determined from the remainder of the estimate of overall relative risk after subtraction of an amount attributable to smoker misclassification. A model is implemented to estimate the overstatement of relative risk due to smoker misclassification, the technical details of which are included in Appendix B. The overall relative risk of lung cancer remains significant after adjustment for smoker misclassification. Based on this outcome and other evidence, it is concluded that ETS is causally associated with lung cancer. After numerically adjusting for background ETS (sources other than spousal smoking), the lung cancer risk of ETS from all sources to the U.S. population of nonsmokers

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(never-smokers and former smokers of both sexes) is characterized in terms of the number of lung cancer deaths (LCDs) attributable to ETS (estimated at 3800).

Several other authors have estimated the population risk of lung cancer from exposure to ETS also. Two approaches have been used almost exclusively. One analyzes the overall epidemiologic evidence available from case-control and cohort studies, as done in this report. The second approach estimates a dose-response relationship for ETS exposure based on "cigarette-equivalents" determined from a surrogate measure of exposure common to passive and active smoking. Cotinine concentrations in body fluids (urine, blood, or saliva) and tobacco smoke particulates in SS and MS have commonly been used for this purpose. The lung cancer risk of ETS is assumed to be equal to the risk of actively smoking at the rate determined by the cigarette-equivalents.

The NRC report is a good example of the first approach. An overall estimate of relative risk (RR) for never-smokers exposed to spousal smoking is obtained by statistical analysis across all available studies (as in Chapter 3 of this report). Two adjustments are made then to the estimate of RR. The first adjustment accounts for expected bias from former smokers (FS) and current smokers (CS) who may be misclassified as never-smokers (NS) and it results in a decrease in the RR estimate. The second adjustment, an upward correction, takes into account the risk from background exposure to ETS (experienced by a NS whether married to a smoker or not). Population risk can be characterized then by estimating the annual number of LCDs among NS attributable to all sources of ETS exposure (spousal smoking and background). This calculation requires the final-adjusted estimate of relative risk, the annual number of LCDs from all causes in the population assessed (e.g., NS of age 35 or above), and the proportion of that population exposed to spousal smoking. The entire population is assumed to be exposed to a background level of ETS.

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The cigarette-equivalents approach calculates an estimate of the lifetime excess risk of lung cancer from exposure to ETS, extrapolated from a dose-response curve constructed for dose-response of active smoking. Multiplying this estimate by the size of the population exposed to ETS characterizes the population risk in terms of the excess number of lifetime lung cancers. It is important to note that the population excess risk in the first approach is stated in terms of an annual number of lung cancer cases; in the second approach, population risk is stated in terms of the lifetime excess number of lung cancers. There are variations on the two basic approaches described, but the published literature largely falls into the two camps described—inference from the epidemiologic studies or extrapolation from a dose-response assessment for active smoking. A recent review of risk assessment methodologies in passive smoking may be found in Repace and Lowrey (1990).

Examples from the published literature illustrating both approaches and their results are reviewed in Sections 4.2 and 4.3. Section 4.4 describes the risk assessment of lung cancer from ETS exposure for this report, based on epidemiologic data (the first approach described above) The overall relative risk to female NS married to a smoker is estimated from the epidemiologic studies with 95% confidence bounds and then an adjustment for smoker misclassification bias is calculated from an extension of the NRC/Wald formula. Background ETS is taken into account in a second adjustment to RR (implicitly redefining RR at that point to be "relative" to the risk at zero-ETS instead of at an average background level of ETS). The population attributable risk then is estimated to obtain an annual number of U.S. LCDs in never-smoking women attributable to total ETS exposure. The predicted number of LCDs due to ETS is further extended to include male NS and then to include former smokers of both sexes.

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4.2. PREVIOUS ESTIMATES OF RELATIVE RISK FROM EPIDEMIOLOGIC DATA

4.2.1. The NRC Report and Wald et al. (1986)

The NRC report follows the construct of Wald and coworkers to adjust for potential misclassification bias. The technical details of the adjustment are contained in Wald et al. (1986) and to a lesser degree in the NRC report. An illustrative diagram for the implicit true relative risk of lung cancer from exposure to ETS in women from spousal smoking is shown in Figure 2 of Wald et al. A similar example is in Table 12-5 of the NRC report. The formula for an extended version of these examples is given in Appendix B (Equation B1), with the required parameters described in Tables B-1 through B-3. The summary relative risks from observed data reported by the NRC are 1.32 (95% C.I. 1,16, 1.51) for females and 1.62 (0.99, 2.64) for males. Both RR estimates apply to NS married to smokers, i.e., the estimates apply to lung cancer risk in exposed NS (actually exposed to spousal smoke and background sources) relative to the risk in unexposed NS (actually exposed to background sources only). The terminology adopted from epidemiologic studies comparing an exposed group with an unexposed group can be misleading when sources of ETS other than spousal smoking are taken into account (i.e., background ETS). Both groups experience background exposure to ETS, so one group is at a higher exposure level (from spousal smoking and background) and the other one is at a lower exposure level (backgound alone).

After adjusting for expected negative (downward) bias in the RR estimates due to smoker misclassification, the NRC concludes that the relative risk for both females and males is likely to be 1.25, and probably lies between 1.15 and 1.35. The "relative" in RR, however, still means relative to the risk from background exposure alone. To estimate the number of LCDs in NS attributable to ETS, risk estimates need to be relative to the risk of lung cancer at zero-ETS exposure instead of at background exposure. This is accomplished in the NRC report by using data on cotinine concentrations to compare exposure to ETS at the higher level (background

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plus spousal smoking) with exposure to the lower level (background only). This report uses the same method; it will be discussed in more detail. The resultant estimates of RR apply to exposed persons and to unexposed persons, but are now relative to risk at zero-ETS instead of risk at the background level. This adjustment for background sources changes the NRC estimate of RR for an exposed person to 1.42 ("ranging" from 1.24 to 1.61); the change is due only to implicit redefinition of RR to mean risk relative to zero-ETS, however, instead of relative to a background level of ETS. Similarly, the RR estimate from background ETS becomes a positive value, since RR now means relative to zero-ETS. The estimates given by the NRC are for both sexes, with the qualification that the adjustment for background and the estimation of LCDs attributable to passive smoking (to be described next) are "crude".

The NRC report estimates that about 21% of the lung cancers in nonsmoking women and 20% in nonsmoking men may be attributable to exposure to ETS (NRC, 1986, Appendix C). When applied to the ACS's estimate of 6500 (3000) LCDs among NS women (men) in 1988, the number attributable to ETS exposure is 1365 (600), a total of about 2000. To obtain these figures for annual LCDs attributable to ETS in NS requires the RR figure for exposed and unexposed persons obtained from data on married NS. Not all NS are married, of course, and the NRC estimates that 17% of all NS women (married or not) and 12% of NS men (married or not) are exposed to ETS at the higher exposure level (equivalent to background plus spousal smoking); the remaining percentages are assumed to be exposed at the lower exposure level (background ETS only). These exposure percentages are based on a sample of cotinine concentrations. In effect, the NRC is estimating the RR for the population of NS by taking a weighted average of the RR at the higher exposure level and the RR at the lower exposure level, weighted by the proportions of the population at the higher and lower exposures. The population is not bipolarly distributed at two exposure levels, but a judicious assignment of values to the proportions assumed will produce a weighted average that approximates RR for

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exposure near the population average. An implicit assumption is that RR is linearly related to ETS exposure between the lower and higher exposure levels.

The remainder of this section discusses details of the NRC and Wald et al. (1986) analyses to adjust the overall RR for bias from smoker misclassification (the first step in the procedure above). In particular, NRC parameter values used for the adjustment are compared with those to be used in Section 4.4 of this report. Both the NRC and Wald et al. assume that 50% of women are NS. Wald et al. assumes that the remaining 50% consists of 35% CS and 15% FS, based on a survey conducted in Britain. Estimates for the U.S. for 1985 from the National Health Interview Survey (NHIS), as reported in the U.S. SG (1989) report, place the percentage of U.S. females who are CS and FS at 27.8% and 16.9%, respectively, for a total of 44.7% ever-smokers (ES) in the U.S. Corresponding values for 1982 from the initial phase of the ACS's Cancer Prevention Study II (CPS-II) are 22.1% and 22.6%, respectively, for the same total percentage (44.7%). Consequently, the 50% value for ES is probably a little high for the U.S., and the composition of female ES in the U.S. between 1982 and 1985 is probably closer to 22% to 28% CS and 17% to 23% FS. In Section 4.4, this report assumes 45% female ES, consisting of 25% CS and 20% FS.

The NRC report estimates that the lung cancer risk of smokers relative to nonsmokers may be as high as 8.0; based on an ACS study in 1966, and the British Physician's Study in 1980, and then allowing for a reasonable increase by the mid-1980s. The initial phase of CPS-II indicates that the relative risk for female CS aged 35 and older has soared from 2.9 between 1959 and 1965 (CPS-I) to 11.9 (95% C.I. 10.0, 14.3) between 1982 and 1986 (CPS-II) (S.G., 1989, p.153). The large change is related to an increase in the number of women who began smoking two to three decades ago, a sufficient period for lung cancers to appear in the mid-1980s. The relative risk reported for female FS in the general population from CPS-II is 4.7 (95% C.I. 3.9, 5.7) U.S. SG, 1989). ES (CS and FS) misreported as NS are assumed to have a

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lower risk than correctly reported ES. The NRC report suggests an overall relative risk of two for misclassified ES (but notes that it could be as high as four). Wald et al. adjusts the smoker's relative risk for misreported CS and FS (from eight to two), assuming the misclassification percentage of ES is an aggregate of 2.1% attributable to CS and 4.9% due to FS.

In this report, calculations for the adjustment to relative risk for misclassification are made directly from the specific values assumed for CS, FS, and NS, without combining CS and FS into a common category (ES). This approach is somewhat more general and should provide additional flexibility and accuracy. The extended formula is given in Appendix B. The calculations in Wald et al. and the NRC report are a special case. Wells has undertaken to model the impact of misclassification in further detail by using parameter estimates that are characteristic of the time and place of each study for which a bias is estimated, e.g., in estimates of relative risk for CS and FS. His initial results indicate that the overall relative risk estimate increases with this modification (personal communication from A.J. Wells).

The NRC report and Wald et al. make a correction to the overall relative risk estimate, using identical procedures, to account for background exposure to ETS. Urinary cotinine is used as a surrogate for recent exposure to tobacco smoke in NS. In the study by Wald and Ritchie (1984), the urinary cotinine levels among NS exposed to smoking spouses were three times those of NS married to NS. To make the lung cancer risk to exposure to ETS relative to a zero-exposure group, it is assumed that the excess lung cancer risk from ETS exposure is proportional to urinary cotinine concentration. Note that this assumption does not imply that cotinine (or its precursor nicotine) determines the carcinogenic potential of ETS. The formula to calculate the adjustment is in Equation B2 in Appendix B.

The NRC report calculates the population-attributable risk, assuming that 17% of nonsmoking women and 12% of nonsmoking men are exposed to ETS and that the remaining percentages are exposed to a background level of ETS (NRC, 1986, Appendix C). The exposure

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percentages for men (12%) and women (17%) are from a sample of cotinine measurements in men reported in Wald and Ritchie (1984). The 17% is a very low figure for female NS when compared to the percentages exposed in the case-control studies (see Figure 3-1). The 121 married males tested by Wald and Ritchie are not representative of the U.S. population. Wald et al. (1986) assume an exposure percentage of 59% in their example calculation for female NS and the NRC report (p.236) uses an odds ratio of 1.3/3.3 (= 39%) for the exposure of female nonsmokers (NS in this case) in its example. In the analysis of this report in Section 4.4, 60% is assumed, with a plausible range from 45% to 75%. These values are reasonable for the case-control percentages in Figure 3-1.

4.2.2. Other Risk Assessments Based on Epidemiologic Data

Wells (1988) provides a quantitative risk assessment that includes several epidemiologic studies subsequent to the NRC and U.S. SG reports. Like the NRC report, the epidemiologic data for both women and men are considered, for which separate estimates of overall risk and attributable risk are provided. The three cohort studies addressed in the NRC report are also included (no additional ones have appeared). Fourteen case-control studies are analyzed, three of which have appeared in the literature subsequent to the NRC report (Brownson et al., 1987; Humble et al., 1987; Lam et al., 1981; denoted in Table 3-1 as BROW, HUMB, and LAMT, respectively). Other differences compared to the NRC report are: WU (Wu et al., 1985) and the study by Sandler et al. (1985) are included; part of the data of BUFF and KABA are excluded; and CHAN is excluded. The reader is referred to Wells (1988) for discussion of criteria for study inclusion.

Wells calculates an overall relative risk of 1.44 (95% C.I. 1.26, 1.66) for females and 2.1 (1.3, 3.2) for males. Following the general approach of Wald et al. (1986), the misclassification percentage for ES is assumed to be 5% (compared to 7% for Wald et al.). Rates were adjusted

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for background exposure to ETS except in studies from Greece, Japan, and Hong Kong, where the older nonsmoking women are assumed to experience very little exposure to ETS outside the home. A refinement in the estimation of population-attributable risk is provided by adjusting for age at death (which also appears in the calculations of Robins [NRC, Appendix D]). The relative risk is calculated under two assumptions regarding risk--constant with age and declining with age, but there is little difference in the two outcomes. A figure of 76% is used for the fraction of female nonsmokers (never-smokers) exposed to ETS, assuming that 60% are exposed to spousal smoking and another 16% are exposed at a comparable level otherwise. The total percentage for males is 61%. The calculation of population-attributable risk applies to FS as well as NS, which is a departure from Wald et al. and the NRC report. The annual number of excess LCDs in the U.S. is estimated to be 1,232 (females) and 2,499 (males) for a total of 3,731. About 3,000, however, is thought to be a best current estimate.

Robins (NRC, 1986 Appendix D) explores three approaches to assessment of lung cancer risk from exposure to ETS, each with attendant assumptions clearly stated. Method 1 is based solely on evaluation of the epidemiologic data applying two assumptions: 1) adjustment of relative risk for background exposure to ETS independent of age, and 2) the excess relative risk in a nonsmoker is proportional to the lifetime dose of ETS. The validity of both assumptions are questioned by the author in later remarks. The age-adjusted population-attributable risk is estimated for females and males separately. (The reader is referred to Robins et al., 1989).

The age-specific fraction of LCDs due to ETS exposure is also required. Data from the controls of one of the case-control studies in the U.S. (Garfinkel et al., 1985) are used for that purpose. The age-specific LCD rates for women are also used in calculating population-attributable risk for males in lieu of no data specific to males. Robins assumes that a relative risk of 1.3 is associated with ETS exposure (1.14, the summary for U.S. studies alone, is also considered). He omits any adjustment for misclassification, but does adjust for background

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exposure. In view of the NRC report's emphasis on the potential for misclassification, this omission is surprising. The author estimates lifetime risk of LCD attributable to ETS, but epidemiologic data alone are not sufficient. Further assumptions implying some similar characteristics in lung cancer risk from active and passive smoking are introduced for that purpose.

Blot and Fraumeni (1986) published a review and discussion of the available epidemiologic studies about the same time as Wald et al. (1986), the NRC, and the U.S. SG reports appeared. The set of studies considered by Blot and Fraumeni are almost identical to those included in the NRC report (see Table 4-1), except for omission of one cohort study (Gillis et al., 1984), and inclusion of WU, the case-control study excluded by the NRC because the raw data were unpublished. An overall relative risk estimate calculated from the raw data for females yields 1.3 (95% C.I. 1.1, 1.5). When the results are combined for high exposure categories, the overall relative risk estimate is 1.7 (1.4, 2.1).

Wigle et al. (1987) apply the epidemiologic evidence to obtain estimates of the number of LCDs in NS due to ETS in the population of Canada. A total of 50 to 60 LCDs per year is attributed to spousal smoking alone, with 90% of them in women. Overall, involuntary exposure to tobacco smoke at home, work, and elsewhere may cause about 330 LCDs annually. The percentage of LCDs in NS used in the calculation is 1.6% for males and 12.4% for females, values obtained by pooling results from U.S. and Canadian reports. The fraction of NS with a smoking spouse is estimated from the control groups in two U.S. studies (Dalager et al. [1986] and the case-control study of the ACS reported in Garfinkel et al. [1985]). A pooled prevalence rate of 40% from these two studies is assumed. The estimated number of deaths from lung cancer attributable to passive smoking is calculated separately for males and females, using age-specific population figures for Canada and age-specific rates of death from lung cancer attributable to ETS (Repace and Lowrey, 1985).

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TABLE 4-1. EPIDEMIOLOGIC STUDIES INCLUDED IN OVERALL RELATIVE RISK IN THIS REPORT (FEMALES ONLY) AND SEVERAL OTHER SOURCES

Study	Sex	Observed relative risk[1]	Sources[2] 1	2	3	4	5
AKIB	F	1.52(0.88,2.64)	F	F	F	F	F
	M	1.80(0.50,5.60)		M	M	M	
BROW	F	1.52(0.39,5.99)			F		F
	M	1.38(- , -)			M		
BUFF	F	0.81(0.34,1.90)		F	F	F	F
	M	0.50(0.20,1.70)		M	M	M	
CHAN	F	0.75(0.43,1.30)	F	F		F	F
CORR	F	2.07(0.82,5.20)	F	F	F	F	F
	M	2.00(- , -)		M	M	M	
GAO	F	1.19(0.82,1.73)					F
GARF	F	1.31(0.87,1.98)	F	F	F	F	F
GENG	F	2.16(1.09,4.28)					F
HUMB	F	2.34(0.83,6.61)			F	F	F
INOU	F	2.55(0.74,8.78)					F
KABA	F	0.79(0.25,2.48)	F	F	F	F	F
	M	1.00(0.20,4.90)		M	M	M	
KOO	F	1.55(0.90,2.67)	F	F	F	F	F
LAMT	F	1.65(1.16,2.35)			F		F

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TABLE 4-1. (continued)

Study	Sex	Observed relative risk[1]	Sources[2] 1	2	3	4	5
LAMW	F	2.01(1.09,3.71)					F
LEE	F	1.03(0.41,2.56)	F	F	F	F	F
	M	1.30(0.38,4.42)		M	M	M	
PERS	F	1.28(0.76,2.15)	F	F	F	F	F
SVEN	F	1.26(0.57,2.81)					F
TRIC	F	2.13(1.19,3.81)	F	F	F	F	F
WU	F	1.41(0.54,3.67)	F		F		F
GARF (Coh)	F	1.18(0.90,1.54)		F	F	F	F
GILL	F	1.00(0.20,4.91)		F	F	F	F
(Coh)	M	3.25(0.60,17.65)		M	M	M	
HIRA	F	1.63(1.25,2.11)		F	F	F	F
(Coh)	M	2.25(1.04,4.85)		M	M	M	

[1] Figures for case-control studies are as recorded in Table 2-5, with the values calculated in this report from raw data used for females. Figures for cohort studies are taken from NRC (1986). Parentheses contain 95% confidence intervals.

[2] Sources are:

1. Blot and Fraumeni (1986).
2. NRC (1986) and Wald et al. (1986).
3. Wells (1988): includes study by Sandler et al. (1985) on women, and the data for males in HUMB (Humble et al., (1987), both of which contain very few cases of lung cancer.
4. Saracci and Riboli (1989).
5. This report.

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Unlike the previous examples discussed, Wigle et al. use the relative risk estimates obtained from a study comparing Seventh-Day-Adventists (SDAs) (Phillips et al., 1980a, 1980b) with a matched group of non-SDAs who are also NS, as reported in Repace and Lowrey (1985). The SDA/non-SDA comparison is used as a basis for assessing lung cancer risk from ETS in a broader environment, particularly outside the home, than the case-control and cohort studies. It provides an independent source of data and an alternative approach for comparison, to be described further in the review to follow.

Repace and Lowrey (1985) suggest two methods to quantify lung cancer risk associated with ETS. The one based on epidemiologic data estimates the relative risk of LCD from all sources of exposure to ETS, i.e., in the home, at work and elsewhere, in what they describe as a "phenomenologic" approach. A comparison of LCDs in the study by Phillips et al. (1980a, 1980b) referred to above, wherein SDA NS and a demographically/educationally matched cohort of non-SDA NS provides the basic data. Information regarding the number of age-specific LCDs and person-years at risk for the two cohorts is obtained from the study. The comparison of two groups of NS is based on the premise that the non-SDA cohort is more likely to be exposed to ETS than the SDA groups due to differences in life-style. Relatively few SDAs smoke, so an SDA NS is probably less likely to be exposed at home by a smoking spouse, or in the workplace, or elsewhere if associations are predominantly with other SDAs. One of the virtues of this novel approach is that it contributes to the variety of evidence for evaluation and provides a new perspective on the topic.

Phillips et al. reported that the non-SDA cohort experienced an average lung cancer mortality rate equal to 2.4 times that of the SDA cohort. Using 1974 U.S. Life Tables, Repace and Lowrey calculate the difference in lung cancer mortality rates for the two cohorts by 5-year age intervals and then apply this value to an estimated 62 million NS in the U.S. in 1979, to obtain a number of LCDs attributable to ETS annually. The result, 4665, corresponds to a risk-

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rate of about 7.4 LCDs per 100,000 person-years. In an average lifespan of 75 years, that value equates to 5.5 deaths per 1000 people exposed.

A recent article by Vainio and Partanen (1989) assumes that the observed relative risk of 1.3 from Wald et al. (1986) represents a causal effect. No adjustment is made for possible misclassification of subjects. The same correction method for background exposure used by the NRC and Wald et al. is applied to the observed relative risk to yield 1.53. Two calculations are made for population-attributable risk applying an excess risk of 0.53 to the exposed fraction of the population of NS and a value of 0.18 for excess risk from background exposure to the remaining fraction. The two calculations are identical aside from the different values of the fraction exposed: 12% (men) and 17% (women) in one case; 28% (men) and 56% (women) in the other. The first pair of values is identical to the fractions used in the NRC report, as discussed previously in this section. The second set is from one of the case-control studies (Humble et al., 1987). The value for population-attributable risk calculated from the exposure percentages 12%, 17%, 28%, and 56%, are 18%, 19%, 22%, and 27%, respectively, which illustrates only moderate sensitivity of the calculations to the different values assumed for the fraction exposed. Vainio and Partanen use the same excess relative risk for both men and women in their calculations. The authors conclude that the proportion of lung cancer cases among nonsmokers that could reasonably be attributed to ETS is 20% to 30%. This range is consistent with population exposure percentages of 20% to 75%. A plausible range for exposure percentages is about 45% to 75% (Section 4.4.2). The approximate range for PAR concluded by Vainio and Partanen is close to what the calculations in this report would be without a downward adjustment of the RR estimate for smoker misclassification bias.

Saracci and Riboli (1989), of the International Agency for Research on Cancer, review the evidence from the three cohort studies and 11 of the case-control studies (Table 4-1). The authors follow the example of the NRC and Wald et al. in the studies to exclude, and add only

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one additional case-control study (Humble et al., 1987). The overall observed relative risk for the studies, 1.35 (1.20, 1.53), is about the same as reported by the NRC, 1.34 (1.18, 1.53). It is not reported how the overall relative risk was calculated.

4.3. APPROACHES TO RISK ASSESSMENT BASED ON CIGARETTE-EQUIVALENTS

The cigarette-equivalents approach assumes that the dose-response curve for lung cancer risk from active smoking also applies to passive smoking, after conversion of exposure to ETS into an "equivalent" exposure from active smoking. For example, suppose the average cotinine concentration in exposed NS is 1% of the average value found in people who smoke 30 cig./day. The lung cancer risk for a smoker of (.01)30 = 0.3 cig./day is estimated by low-dose extrapolation from a dose-response curve for active smoking, and that value is used to describe the lung cancer risk for ETS exposure. This general explanation describes the nature of the approach; however, authors vary in their constructed solutions and level of detail. The basic assumption of cigarette-equivalents procedures is that the lung cancer risks in passive and active smokers are equivalently indexed by the common measure of exposure to tobacco smoke, i.e., a common value of the surrogate measure of exposure in an active and a passive smoker would imply the same lung cancer risk in both.

A difficultly in assessing this approach lies in evaluating the assumption that apparent differences between passive and active smoking are negligible or have cross-effects that cancel. For example, MS and SS differ in the relative composition of carcinogens identified in tobacco smoke and in their physicochemical properties in general. The lung and systemic distribution of chemical agents common to MS and SS are affected by their relative distribution between the vapor and particle phases, which differs between MS and SS and changes with SS as it ages. Passive and active smoking also differ in characteristics of intake--intermittent (possibly deep) puffing in contrast to normal (shallow) inhalation. To help illuminate relationships and identify

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parameters where additional information would be helpful on this topic, a mathematical model for comparison of dosimetry of passive and active smoking was constructed as a basis for further study (Appendix C).

Several authors have taken issue with the validity of the cigarette-equivalents approach. For example, Hoffmann et al. (1989), in discussing the longer clearance times of cotinine from passive smokers than from active smokers, concludes "The differences in the elimination time of cotinine from urine preclude a direct extrapolation of cigarette-equivalents to smoke uptake by involuntary smokers." A recent consensus report of an IARC panel of experts (Saracci, 1989, p.3) states that "Lacking knowledge of which substances are responsible for the well established carcinogenic effect of MS, it is impossible to accurately gauge the degree of its similarity to ETS in respect to carcinogenic potential." The U.S. SG report devotes a three page section to the concept of cigarette-equivalents, quantitatively demonstrating how they can vary as a measure of exposure (U.S. SG, 1986). It concludes with "These limitations make extrapolation from atmospheric measures to cigarette-equivalents units of disease risk a complex and potentially meaningless process." On a lesser note, it has generally been assumed that the dose-response relationship for active smokers is reasonably well understood. Recent literature raises some questions on this issue (Moolgavkar et al., 1989; Gaffney and Altshuler, 1988; Freedman and Navidi, 1987a, 1987b; Whittemore, 1988).

The cigarette-equivalents approach has some important limitations, due in large part to limited knowledge regarding similarities and differences between passive and active smoking and how to adjust for them in a risk assessment. Legitimate reservations not withstanding, virtually all analytic approaches bear some assumptions and weaknesses, and most contribute something to our understanding. Further development of the cigarette-equivalents approach and the knowledge base surrounding it may be worthwhile. Three new methods akin to cigarette-equivalents approach are described in Appendix D, with comments and advice solicited. Several

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published examples of the cigarette-equivalents approach follow. Although a risk assessment based on the epidemiologic data is preferred in this report, it is worthwhile to consider the spectrum of methods and approaches that have been tried.

Vutuc (1984) estimates that exposure of passive smokers to cigarette smoke is equivalent to 0.1 to 1.0 cig./day actively smoked. This relationship follows Repace and Lowrey (1980), except that Vutuc adjusts their figures to apply to a cigarette with tar content of 16 mg instead of 0.55 mg, as assumed by Repace and Lowrey. For the smoking situations indicated by Repace and Lowrey, who found passive smoking equivalent to actively smoking 5 to 27 cig./day, Vutuc obtains an equivalent of actively smoking 0.2 to 1.0 cig./day.

Citing cigarette-equivalents calculated in other sources, Vutuc assumes a range of 0.1 to 1.0 cig./day for ETS exposure. Relative risks for nonsmokers are calculated for 10-year age intervals (40 to 80) based on the reported relationships of dose, time, and lung cancer incidence in Doll and Peto (1978). Relative risks for smokers of 0.1 to 1.0 cig./day give a range in relative risk from 1.03 to 1.36. The author concludes that "As it applies to passive smokers, this range of exposures may be neglected because it has no major effect on lung cancer incidence." As observed by the author, however, the influence of ETS on lung cancer incidence becomes more marked in the higher age groups, where the carcinogenic effect of tobacco smoke is strongly influenced by the duration of exposure. From Vutuc's Table 1, the increase in incidence (per million) in lung cancer for a smoker of one cig./day is 270 at age 79, 130 at age 70, 40 at age 60, etc. These values of risk slightly exceed the acceptable levels typically used by the EPA and other regulatory agencies in setting standards for pollutants under their authority.

Vutuc assumes that his figures apply to both males and females. If an exposure fraction of 75% is assumed for both males and females, the range of relative risks given correspond to a range for population-attributable risk. The number of LCDs among NS in the U.S. in 1988 is about 6500 females and 3000 males (personal communication from the ACS). The number of

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LCDs in NS attributable to ETS is estimated to range from 240 to 2020 (140 to 1380 for females alone). So Vutuc's figures are consistent with several hundred excess LCDs among NS in the U.S. These figures are from our extension of Vutuc's analysis, however, and are not the claim of the author.

Methods 2 and 3 of Robins (NRC, Appendix D) are constructs of the cigarette-equivalents approach. In both methods, a range of values is reported corresponding to a range of unknown parameter values. Method 2 uses an overall relative risk value based on epidemiologic data, but also makes some assumptions to appeal to results of Day and Brown (1980) and Brown and Chu (1987) on lung cancer risk in active smokers. The author estimates the number of excess LCDs due to ETS, assuming 7000 and 5200 annual LCDs in female and male NS, respectively. Adjusting his results to 6500 females and 3000 males (for comparison purposes), the range of excess LCDs attributable to ETS is 1650 to 2990 for females and 420 to 1120 for males.

Robins' Method 3 ignores the epidemiologic data on passive smoking entirely and extrapolates from data on active smoking, along with several assumptions. Applying his results to 6500 females and 3000 males, the range of excess LCDs due to ETS is 550 to 2940 for females and 153 to 1090 for males.

Arundel et al. (1987) attribute only five LCDs among female NS to ETS exposure. The corresponding figure for males is seven (both figures are adjusted to 6500 females and 3000 males). The expected lung cancer risk for NS is estimated by downward extrapolation of the lung cancer risk/mg of particulate ETS exposure for CS. Their premise is that lung carcinogenicity of ETS is entirely attributable to the particulate phase of ETS, and the consequent risk in passive smoking is comparable to active smoking on a per mg basis of particulate ETS retained in the lung. If the vapor phase of ETS were also considered, the number of LCDs attributable to ETS would likely increase.

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Russell and coworkers (1986) use data on urinary nicotine concentrations in smokers and nonsmokers to estimate exposure and risk from passive smoking. The risk of premature death from passive smoking is presumed to be in the same ratio to premature death in active smokers as the ratio of concentrations of urinary nicotine in passive to active smokers (about 0.007). Calculations are made using vital statistics for Great Britain and then extrapolated to the United States. The latter estimate, 4000+ deaths/year due to passive smoking, is for all causes of death, not just LCDs.

Repace and Lowrey (1985) describe a cigarette-equivalents approach as well as the procedure described previously. One objective is to provide an assessment of exposure to ETS from all sources that is more inclusive and quantitative than might be available from studies based on spousal smoking. They consider exposure to ETS both at home and in the workplace, using a probability-weighted average of exposure to respirable suspended particulates (RSP) in the two environments. Exposure values are derived from their basic equilibrium model relating ambient concentration of particulates to the number of burning cigarettes per unit volume of air space and to the air change rate. From 1982 statistics of lung cancer mortality rates among smokers and their own previous estimates of daily tar intake by smokers, the authors calculate a lung cancer risk for active smokers of 5.8×10^{-4} LCDs/year per mg tar/day per smoker of lung cancer age. The essential assumption linking lung cancer risk in passive and active smokers is that tobacco tar inhaled poses the same risk to either on a per unit basis. Extrapolation of risk from exposure levels for active smokers to values calculated for passive smokers is accomplished by assuming that dose-response follows the one-hit model for carcinogenesis. An estimated 555 LCDs per year in U.S. nonsmokers (NS and FS) is attributed to ETS exposure (for 1980). The ratio of total LCDs in 1988 to 1980 is approximately 1.37 (Repace, 1989). With that population adjustment factor, the approximate number of LCDs attributable to ETS among nonsmokers is closer to 760 for 1988 (including FS).

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The potential for bias due to misreported smoking habits was apparently first noted by Lee (see discussion in Lehnert, 1984), and has been emphasized by him in several articles, e.g. Lee (1986, 1987a, 1987b). In Lee (1987b), it is argued that smoker misclassification may explain the entire excess lung cancer risk observed in self-reported NS in epidemiologic studies. A hypothetical example is first provided to the reader to illustrate that if 5% of reported nonsmokers are actually smokers, and the relative risk of lung cancer of smokers to nonsmokers is 20, then a relative risk as high as 1.75 could be observed for ETS exposure to spousal smoking. The example is a little misleading in view of the discussion that follows in the article on the results of three separate studies aimed at measuring the accuracy of reported current smoking (a cotinine study), the accuracy of reported lifetime smoking (a 1980/1985 follow-up study), and concordance of smoking habits in married couples (a 1985 consumer study). ("Marriage aggregation factor" in NRC [1986] and Wald et al. [1986] is a measure of concordance). All three studies were conducted on British or UK subjects ages 16 and above. Following review of these studies, the author assumes more refined parameter values.

The relative risk for smoking is assumed to be 10 instead of 20. The evidence suggests that about 1.4/2.5 (56%) of misclassified CS may be regarded as "regular smokers" and 1.1/2.5 (= 44%) as only "occasional smokers." The relative risk of the latter is assumed to be 2.5 instead of 10. Based on cotinine measurements, 20 of the 689 self-reported NS (2.9%) are treated as CS, 9 as occasional and 11 as regular smokers. (In the notation of Table B-1, this equates to RR(E/C) = 6.7). The relative risk of misclassified FS is assumed to be 2.0 (giving RR(E/F) = 2.0 in Table B-1). The percentage of reported NS assumed to be FS is 10, equivalent to 21% of the (true) FS. No supporting evidence was found for the 10% figure for FS, but the follow-up study does provide evidence that the percentage may be lower for women than men. Applying an adjustment for women to the 10% and 21% figures above gives 2.8% and 7%, respectively, for

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women. (This correction for estimation of risk to women was of little consequence to our calculations.)

The remaining parameter values from Lee (1987b) needed to apply the formula for adjustment to misreporting bias in Equation B1 are as follows, where the variable identifiers are described in Table B-2: (V1,0.336), (V4,0.025; 0.011 for regular smokers plus 0.014 for occasional smokers), (V5,0.483), (V8,0.181), (V11,0.10), (V16,6.7; from a RR of 10 for CS and 2.5 for FS), and (V20,2.0). The observed relative risk for a true value of one from Equation B1 is 1.18. With the correction for women described, 1.18 would be reduced to 1.16. These values are close to what the NRC report and Wald et al. calculated for an expected value of the observed relative risk when the true value is one. The excess above one is the anticipated bias for smoker misclassification.

Assuming that the parameter values specified above accurately reflect the author's description, the method of adjusting for misclassification detailed in Appendix B (adapted in principal from Wald et al. [1986] and the NRC [1986]) does not support the claim that self-reported misclassification would fully account for the excess risk of lung cancer observed in the epidemiologic data. The lower 95% confidence limit on the overall summary observed relative risk of 1.40 is 1.25, and the 99% lower limit is 1.21, still above the range potentially explained by the misreporting of smoking habits alone.

The study results discussed by Lee for setting parameter values need to be included in the larger pool of related information and study evidence available, particularly for inference on U.S. women of age 35+. It appears likely that there are sex-related differences in rate of misreporting, and possibly in other parameters. Age may be a factor. It has not been indicated whether persons of ages 16 to 30, too young to be included in epidemiologic studies, are representative of the older age groups in terms of rates of misreporting and other factors. When

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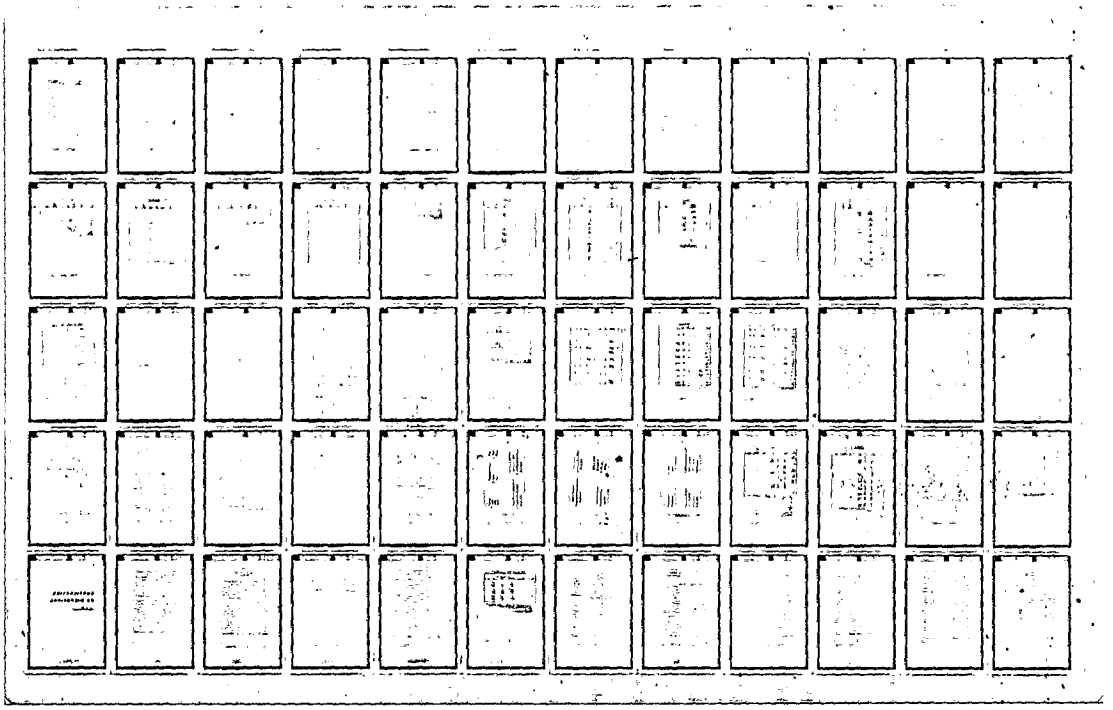
ETS, EPA (3)



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only 20 out of 808 reported nonusers of tobacco are reclassified as CS (11 as regular users at a relative risk of 10 or so), a few subjects may have a large impact on the outcome.

Several further observations on this article may be noted. It is concluded that the overall observed relative risk from spousal smoking to ETS can be explained as bias due to probable overstatement of the number of reported NS. It would follow that the true excess risk is zero. Extrapolation of risk from active smoking using average cotinine concentration in smokers and NS married to a smoker, however, is recommended in place of analysis of the epidemiologic data. It is concluded that there is a positive excess risk to ETS exposed NS (1.02 for women and 1.07 for men). As discussed previously, values in this range cannot be regarded as negligible.

4.4. CURRENT ASSESSMENT OF LUNG CANCER RISK

The data from epidemiologic studies currently available are evaluated for evidence of an elevated occurrence of lung cancer associated with ETS exposure. The methodological approach of Wald et al. (1986) and the NRC report are adapted with two minor modifications. The adjustment for relative risk of ES is calculated by its separate components (CS and FS). The second modification is to distinguish between parameter values for "reported" and "correct" classifications. Some parameter estimates depart from values used by the NRC, largely reflecting more current evidence and information available in some areas (Section 4.4.2). The most significant difference in parameter values is probably in the relative risk of active smoking. The value of eight assumed by the NRC is replaced by 12 (from the ACS's Study CPS-II, as reported in U.S. SG [1989]). Following the adjustment to an overall relative risk estimate for misclassification, a further adjustment is made to account for background exposure, i.e., for exposure to NS aside from spousal smoking, the dominant measure in the epidemiologic studies to distinguish between exposed and unexposed subjects.

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The twice-adjusted RR estimate is combined with the percentage of the population exposed to ETS to obtain an estimate of the population-attributable risk (PAR), the proportion of LCDs in female NS of age 35 and older attributable to ETS exposure. Upper and lower confidence limits on the PAR are determined. These limits are conditional on the population exposure percentages assumed. Multiplying the PAR by the number of LCDs in never-smoking women in 1988 estimates the excess number of LCDs attributable to ETS.

In the final section of this chapter the population-attributable risk is calculated separately for each of the 19 case-control studies with data available and the three cohort studies, using the exposed fraction of controls from each study in the calculations. The ordered outcomes provide a basis for reviewing similarities/dissimilarities between studies, such as the country of origin and other study characteristics shown in Chapter 3. Although it is likely that the true differential in ETS exposure for subjects classified as exposed or unexposed is relatively higher in some sampled human environments than others (probably higher in Japan, for example, as discussed by Hirayama and others), comparison of outcomes with study characteristics did not reveal any apparent patterns or study characteristics associated with the findings.

4.4.1. Combining Evidence Across Studies

The overall relative risk estimate for case-control studies is determined by the extended Mantel-Haenzsel procedure. The M-H method was applied to case-control studies in Chapter 3 to test for an association between ETS and lung cancer. This same method is now applied to the raw data of case-control and cohort studies to obtain an overall estimate of RR and confidence interval. The procedure used in the NRC report (1986, Appendix B) is basically this same method (Yusuf et al., 1985). The method of combining cohort studies, and then obtaining an overall value for case-control and cohort studies together, follows the NRC procedure.

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The case-control studies included in the analysis and their observed relative risks from raw data are in Table 4-1 (also see Table 3-5). Two studies, SHIM and VARE are excluded because the raw data were not available. The overall estimate of relative risk for the 19 case-control studies and three cohort studies in Table 4-1 is 1.41 (95% C.I. 1.26, 1.57). This value may be compared to 1.32 (1.16, 1.51) in the NRC report for females (three cohort studies and ten case-control studies), and to 1.50 (1.3, 1.8) determined by Wells (1986) from three cohort studies and 14 case-control studies. The shortest confidence interval is for the analysis of this report, indicating that the additional studies since the NRC report have reduced the statistical uncertainty in the estimated RR as would be anticipated. The higher estimate of relative risk in Wells' analysis is largely due to the choice of studies. The study designated as CHAN, reporting a relative risk value of only 0.75, was excluded by Wells but was included in the NRC report and in our analysis.

The summary RR of 1.41(1.26, 1.57) in this report is from the combined values of 1.42 (1.24, 1.63) for 19 case-control studies and 1.39 (1.15, 1.67) for three cohort studies. These figures are almost identical, so the results of one type of study reinforce the outcome from the other type. The consequence of combining the two summary outcomes is essentially just to shorten the confidence interval which is equivalent to reducing the standard error of the estimate of RR. For U.S. studies alone, the RR is 1.25 (1.03, 1.52), the combined RR from seven case-control studies is 1.34 (1.00, 1.79), and GARF(coh) is 1.18 (0.90, 1.54).

Adjustment for smoker misclassification, using the method and parameter values described below, reduces the overall observed relative risk of 1.41 (1.26, 1.57) to 1.28 (1.12, 1.45). Modification for background exposure to ETS raises it to 1.48 (1.21, 1.87). The NRC committee, with eight fewer case-control studies, obtained an overall summary value of 1.34 (1.18, 1.53) for both men and women that was adjusted to 1.25 (with 1.15 to 1.35 possible) for misclassification, and then to 1.42 ("ranging" from 1.24 to 1.61) for background exposure. The

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values for women alone should be only slightly lower judging from the initial overall relative risk of 1.32 for women.

4.4.2. Adjustment To Relative Risk for Smoker Misclassification

The reduction formula for misreporting current smokers (CS) and former smokers (FS) as never-smokers (NS) is described in Appendix B. The general equation (B1) is accompanied by a description of parameters in Tables B-1 and B-2. Alternative specification of parameters in terms of "reported" and "correct" values is sometimes useful. The algebraic relationships for this conversion are shown in Table B-3. The description of parameter values used to adjust for smoker misclassification in this report follows, with variable identifiers in parentheses for use with Table B-2.

The percentages of reported CS, FS, and NS are 21.3, 24.0, and 54.7, respectively (V12, V13, V15). These values are obtained from the ACS's study CPS-II (Stellman and Garfinkel, 1986) except that 3% of the reported "never-smoked regularly" (56.4%) were reclassified as FS, leaving 54.7% estimated NS (see footnote d, Table 2, of U.S. SG [1989])., The NRC report and Wald et al. (1986) use 25%, 15%, and 50% for CS, FS, and NS, respectively, from a study of smoking habits in the U.K.

The percentages of reported NS who are misclassified as CS and FS are 2 (1.5, 2.5) and 4 (2, 6), respectively (V1, V2), where the parenthetical values denote a reasonable range. Wald et al. describe evidence to support values of 1.6% and 4.9% for these parameters respectively. Lee (1987b) makes a case for 2.5% (1.1% for regular smokers and 1.4% for occasional smokers) and assumes 10% for misclassified CS and FS, respectively (both males and females.) Adjusting the 10% value to reflect a lower rate of misreporting by females (Lee, 1987b) would make it 2.8%. Cummings (1989b) found that six subjects of a total 669 (1%) reported NS and FS were misreported CS (urinary cotinine above 90 mg/dL). Jarvis et al. (1984) found that 21 of 121

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reported nonsmokers (17%) were CS based on biochemical markers. This very high rate was found among elderly patients attending clinics for smoking-related disease, whose doctors had frequently urged them to give up smoking.

The percentages of misclassified CS and FS who are exposed (married to a smoker) are both 82 (71, 92) (V5, V6). These values correspond to an exposure percentage of 60 (45, 75) (V4) for reported NS, and a marriage aggregation factor (MAF) of 3.07 for females (from Lee, 1987b). (The MAF is the ratio of cross-products, i.e., the odds ratio, in a 2-by-2 table of smoking status of subject by smoking status of spouse. The MAF is assumed to be the same for NS compared with either CS or FS). Table 12-7 of the NRC gives MAF = 3.1 for females, a value communicated from Wald et al. The NRC report considers values of 2.5, 3.5, and 4.5, with 3-4 likely.

Evidence suggests that CS and FS who are misclassified as NS are likely to be only light smokers and that misclassified FS have typically stopped smoking several years previously (Wald et al., 1986). Estimates of relative risk for CS and FS (females) are 11.94 (9.99, 14.26) and 4.69 (3.86, 5.70) for 1982-1986 (ACS's CPS-II Study, as reported in U.S. SG [1989]). Our report assumes the relative risks of misclassified CS and FS are 5.95 (5.0, 7.15) and 2.97 (2.7, 3.86) (V7, V8), respectively (discussed and compared with other sources below). If exposed, the values are incremented by the excess risk from exposure to ETS (1-V(9)) to obtain variables V10 and V11. (Technical Note: Equation (B1) is implemented by setting a value for V(9) along with other parameters to obtain a corresponding value of RRO. To find the value of RRM that corresponds to a specific value of RRO may require a few iterations from the starting point chosen for RRM.)

Parameter values for the RR of CS and FS misreported as NS have been determined in other sources from the information available for the relative risk of smokers and FS in general. To compare our parameter values of the RR for CS and FS misclassified as NS with those of

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other authors, their formulas for reducing the RR of CS and FS who are misreported NS have been applied to the RR figures from the CPS-II survey given above. For misclassified CS, the results are--NRC (1986): the range from 3.0 to 6.0; Wald et al. (1986): 3.8(3.3, 4.3); Wells (1988): 4.6(4.0, 5.4); and Lee (1987b): 8.0(6.7, 9.6). All but the last entry are below the value 6.0(5.0, 7.2) in this report. For misclassified FS, the figures in these sources would be--NRC: the range from 3.0 to 6.0; Wald et al.: 1.9(1.8, 2.1); Wells: 1.9(1.8, 2.1); Lee: 3.0(2.5, 3.6). The last entry is comparable to 3.0(2.7, 3.9) of this report.

4.4.3. Parameter Sensitivity

For the parameter values described above for this report, a true relative risk of 1.00 corresponds to an observed relative risk of 1.14, a 14% inflation due to smoker misclassification. For each of the parameters with a range of input values (shown in parentheses), the lower and upper values in the parentheses were also applied, leaving the other parameter values fixed. The marriage aggregation factor varied between 2.0 and 4.0 as well. The observed relative risk did not exceed 1.19. The 95% lower confidence limit on the overall observed relative risk from the epidemiologic data is 1.25, still well above the likely range explained by misclassification. (The 99% lower confidence limit is approximately 1.21, still above the explainable range). Only one parameter was set at an extreme value at one time in the sensitivity testing, and it is not improbable that some combination of parameters chosen this way would produce a value exceeding 1.25. But the observed risks from the epidemiologic data appear unlikely to be explained by misclassification alone, and no single parameter within a plausible range alters that conclusion.

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4.4.4. Adjustment to Relative Risk for Background Exposure

The relative risk of ETS in epidemiologic studies is relative to the baseline risk of a female NS married to a nonsmoker, who still has some background level of exposure to ETS. Some assumptions are required to approximate the lung cancer risk due to background exposure to ETS. A means of estimating the proportion of total ETS exposure that is due to background in an exposed individual (actually exposed to background and to spousal smoke) is needed. The NRC report compared average cotinine concentrations in exposed and unexposed persons. Assuming that lung cancer risk from passive smoking is linearly related to cotinine concentrations at these low doses, lung cancer risk of passive smoking can be estimated at the higher exposure level (background plus spousal smoking, applicable to an exposed person) and at the lower exposure level (background only, applicable to an unexposed person), with both estimates relative to the risk of lung cancer risk from zero exposure to ETS.

Background ETS appears to constitute about one-third of the total ETS exposure of a NS married to a smoker, if cotinine concentrations are used as an index of total exposure. The ratio of average cotinine concentrations in exposed to unexposed married NS is assumed to be three in the NRC report, based on evidence from Wald and Ritchie (1984). The Wald and Ritchie study applies to men, but Lee (1987b) reports a ratio of 1/.3 (= 3.3) in women and Coultas et al. (1986) report a ratio of 3.41/1.45 (= 2.35) from saliva cotinine levels in a population-based survey of Hispanic subjects in New Mexico. Three is used in this report (X = 3 in Equation B2), along with the assumption that cotinine is a constant multiple of the carcinogenic potency of ETS at low doses. Applying the method used by the NRC (Appendix B of this report) to take background exposure into account changes the overall RR estimate adjusted for misclassification from 1.28 (1.12, 1.45) to 1.48 (1.21, 1.87) for female NS. It should be noted that the meaning of RR is changed with this adjustment--from meaning relative to the risk from background ETS to meaning relative to the risk at zero-ETS exposure. (Note: There

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is an important distinction between the use of cotinine as a surrogate dose for ETS to estimate lung cancer risk from background exposure and its use in the cigarette-equivalents approach (Section 4.3). In the latter, the contention centers around the assumption that cotinine (or anything else, such as respirable suspended particles) is an equivalent dose surrogate for both passive and active smoking, i.e., that equivalent uptake in passive and active smoking implies equivalent carcinogenic risk.)

4.4.5. Population-Attributable Risk and Excess Lung Cancer Deaths

The number of LCDs in U.S. female NS in 1988 is estimated to be 6500 (3000 for male NS). The 6500 figure includes both married and unmarried NS. The ACS's CPS-II Study (reported in Stellman and Garfinkel, 1986) percentages for marital status of all women surveyed (not just NS) are: married, 75.3; divorced 5.1; widowed, 14.6; separated, 0.8; and single, 4.2. Our estimates of risk apply to married female NS, about 75% of female NS, so it is necessary to consider exposure to ETS in the remaining 25% of unmarried NS.

Cummings (1989b) obtained urinary cotinine levels on a total of 663 self-reported NS and FS. The cotinine levels were only slightly higher in males than females (9.6 and 8.2 ng/mL, respectively), and slightly more than half of the subjects were females. The average cotinine level (in ng/mL) was 10.7 for married subjects if the spouse smoked and 7.6 otherwise (all units in ng/mL). Interestingly, the average cotinine levels reported by marital status are: married, 8.3; never married, 10.3; separated, 11.8; widowed, 10.4; and divorced, 9.2. The study, which includes 7% of age 18 to 29, and 47% of age 60 to 84, does not claim to be representative. Nevertheless, the results suggest that in terms of ETS exposure, an unmarried NS is probably closer, on average, to a NS married to a smoker (an exposed person) than to a NS married to a nonsmoker (an unexposed person). This observation is also consistent with the findings of Friedman et al. (1983).

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The percentage of married female NS who are married to smokers is assumed to be 60, with a plausible range of 45 to 75 (Section 4.4.2.). The choice of exposure percentages is based on the distribution of values observed in the epidemiologic studies (Table 3-2 and Figure 3-1). From the discussion of exposure to unmarried female NS above, it is reasonable to assume that exposure to ETS, on average, is at least as large as the sum of 60% of the higher exposure level (from spousal smoking plus background) and 40% of the lower exposure level (background alone) experienced by a married female NS. For the calculations needed from these figures, this assumption is equivalent to treating unmarried and married female NS alike, in terms of exposure to ETS (60% exposed at a level equivalent to spousal smoking plus background and 40% exposed at the background level). Alternatively, average exposure in the population of female NS (including marrieds and unmarrieds) is assumed to be at the background level plus 60% of the exposure from spousal smoking. The percentages assumed by others in the literature have varied: 82 (Lee, 1987b), 76 (Wells, 1988), 59 (Wald et al., 1986), and 17 (NRC, 1986). The NRC percentage was taken from a sample of urinary cotinine bioassays appearing in Wald and Ritchie (1984). The 17% figure is likely much too low to be representative of the population of interest.

The population-attributable risk (PAR) for women is the proportion of LCDs in female NS per year associated with exposure to ETS. Multiplying it by the total number of LCDs in female NS gives the number of excess LCDs per year from ETS exposure, i.e., the number attributable to ETS exposure. For calculation of PAR in this report, the percentage of NS exposed to ETS is assumed to be the same for marrieds and unmarrieds (60% as discussed above). The PAR for the 60% assumption in women is 0.27 (95% C.I. 0.14, 0.41). (Technical Note: The calculations are from Equation B3 with P(E/N) = 0.6, RRM = 1.28 and RRB = 1.48. The confidence interval is calculated by using the upper and lower confidence bounds for RRM and RRB in Equation B3. The confidence interval is conditional on the exposure

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percentage of 60%). Multiplying the PAR by 6500, the number of LCDs in female NS in 1988, gives 1750 (910, 2660) estimated LCDs in female NS in 1988. The number of LCDs in male NS is probably about one-half the number of females, although the evidence for males is scant in comparison to females. The available data indicate that the risk to male NS is not likely to be smaller than for female NS. Applying the PAR value of 0.27 to the total number of LCDs in male NS (3000), gives an estimate of 810 LCDs per year in male NS due to passive smoking. For both sexes combined, the annual number of LCDs in NS attributable to ETS exposure is about 2500, with a range of 1300 to 4000.

A figure for FS also needs to be included in the estimate of LCDs attributable to ETS since they constitute a large segment of the population. Repace and Lowrey (1985) and Wells (1988b) estimated the risk to FS. Sandler et al. (1985) and Geng et al. (1988) found, respectively, an increased total cancer risk and an increased lung cancer risk in active smokers as a result of passive smoking. Sandler et al. found that relative to active smokers who had no other smokers at home, smokers who had one, two, or three or more smokers at home had increased risks of (total) cancers of 40%, 120%, and 160%, respectively. To calculate the annual number of LCDs in FS attributable to ETS, RR is assumed to be the same for FS and NS. The figure calculated for FS is 1260 (540 women and 720 men), making the yearly total of LCDs attributable to ETS approximately 3800. Data on the number of FS in the U.S. population and the calculational details are included in Appendix B.

The 3800 figure is based on a population exposure percentage of 60, the mid-point in a plausible range of 45% to 75%. The results, however, are not very sensitive to the exposure percentage. If 45% (75%) is assumed instead of 60% in the preceding calculations, then the yearly total of LCDs attributable to ETS is approximately 3500 (4100) instead of 3800. This range, 3500 to 4100, corresponds to the plausible range of the exposure percentage, 45% to 75%, for the estimate of RR after adjustment for misclassification (RRM = 1.28) and correction

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for background exposure to ETS (RRB = 1.48). The RRM and RRB figures are based on the epidemiologic studies of female NS married to smokers and the simple linear model using cotinine concentrations to account for background exposure to ETS. Ninety-five percent confidence intervals are available for the population values of RRM and RRB, given by (1.12, 1.45) and (1.21, 1.87), respectively. Calculating PAR from the low (high) value of the plausible range of exposure percentages, 45% (75%), and low (high) values of the 95% confidence intervals for RRM, 1.12 (1.21), and RRB, 1.21 (1.87), provides estimates that are probably too low (high). Using these values to recalculate the population risk provides numerical markers for low and high extremes of the estimated number of LCDs due to ETS. These markers are approximately 1800 and 6100.

In summary, the estimated total number of LCDs per year due to ETS exposure is 3800. It is approximately the sum of estimates for NS females (1750), NS males (810), FS females (540), and FS males (720), assuming a 60% exposure rate. Using the lower (upper) confidence limits for RRM and RRB and the lower (upper) end of the plausible range for exposure percentage gives approximately 1800 (6100) total LCDs per year due to ETS. These low (high) totals consist of NS females 820 (2800), NS males 380 (1290), FS females 250 (860), and FS males 330 (1150). Characterization of the population risk is based on data for female NS from 22 epidemiologic studies of varied design and protocol conducted in numerous locations under ordinary environmental conditions. Extension of these results to the population of all U.S. nonsmokers is not without uncertainty, but is probably conservative. It is unlikely that the true number of LCDs per year in U.S. nonsmokers lies outside the interval defined by the two extreme values, 1800 and 6100.

4.4.6. Adjusted Relative Risk and Population-Attributable Risk by Individual Study

The estimates of RR for lung cancer from ETS exposure have been statistically combined

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to give an overall estimate and confidence interval. The overall observed value (RRO) was adjusted for possible misclassification (to be called RRM) and for background exposure to ETS (to be called RRB). The latter "correction" was to make the risk estimates relative to zero-exposure.

Combining results from all studies increases the statistical power to detect an exposure effect on lung cancer. Aside from weighing each study's results according to a measure of statistical uncertainty (influenced but not solely determined by sample size), studies are treated as if they were qualitatively equivalent and as if the "true" RR were the same in all environments studied. Qualitative differences exist in all studies, but there is little basis for quantifying them. The true values of RR being estimated depend on both the study design and protocol. Culture, environment, and life-style would influence inter-study differences. In particular, one might expect these factors to contribute to inter-country variability in the epidemiologic data. To extract this source of variability statistically would require multiple studies, similar in design and execution, from each country. Although there is more than one study from several countries among those analyzed (China [2], Hong Kong [4], Japan [2], Sweden [2], U.S. [8]), the studies are not sufficiently similar within countries to test variability. In particular, there is considerable dissimilarity between the U.S. studies, and this probably contributes to their wide ranging results.

The observed relative risk from each study is adjusted for misclassification and background rate and the PAR is calculated to evaluate the dissimilarity of results. The percentage of exposed NS for a study is taken from the observed percentage among controls of the study (Table 3-2 or Figure 3-1). The exposure percentages for CS and FS are then calculated assuming a marriage-aggregation factor of 3. The same exposure parameters are used in both the calculations of misclassified smokers and the population-attributable risk.

By using 95% confidence limits on the RR estimate for each study in the calculations,

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limits are obtained for the PAR. Interpretation of these limits is conditional on the percent exposed, which is a random variable. Aside from the exposure percentages described above, the values and method of calculation are the same as used previously in Section 4.4. The results of adjusting each study's observed relative risk for misclassification are shown in Table 4-2. (Technical Note: The overall observed RR, denoted by RRO, is corrected for misclassification (RRM) and then for background exposure (RRB). The excess RR for background exposure is approximately RRB - RRM, which applies to all NS. The additional excess risk to the proportion of NS exposed to ETS equals RRM-1.) A minus sign (-) in Table 4-2 indicates that the observed excess risk after adjustment for misclassification is negative, i.e., the adjusted RR < 1. The adjustment for misclassification decreases as the observed relative risk increases and is treated as negligible for values above 2.5. The observed value that would correspond to a true RR of one was also calculated for each study. These range from 1.12 (BUFF) to 1.22 (BROW), and cluster from 1.13 to 1.16. The excess risk from background exposure to ETS shown in Table 4-2 was arbitrarily limited to 0.2. When the excess risk after adjustment for misclassification is zero, a correction for background is not appropriate. The values for PAR have associated confidence intervals predominantly with a lower limit of zero (the minimum) and an upper limit in the range 34% to 75%. Exceptions include the case-control studies CHAN and TRIC, and the cohort study HIRA, with percentages of (0,13), (3,58), and (14,49), respectively.

The estimates of PAR and their upper confidence limits are rank-ordered in Table 4-3. Probable values are shown for three studies in which the calculation could not be made due to insufficient data. The studies with a zero estimate of PAR were reviewed to see if some common characteristic might be apparent. Remarks about some of those specific studies follow. The studies with an estimate of zero PAR will serve to indicate some possible sources of disparity in results across other studies as well.

WU includes only patients with adenoma (ADC) or small cell carcinoma (SCC) of the

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lung in their case groups. Their results overall are somewhat ambiguous regarding ETS exposure, which the authors attribute to the lesser etiologic role of ETS for ADC compared to SCC. The number of SCC observed, however, was too small to warrant quantitative comparisons. Of 29 ADC cases, 12 are bronchoalveolar cell carcinomas, which Correa et al. (1983) found to have only a weak association with passive smoking. GILL(Coh) reports that insufficient time had elapsed since completion of the recruitment phase of their cohort study to observe a sufficient number of cases to allow firm conclusions. Only six instances of lung cancer in exposed females had occurred. In BUFF, exposure refers to having ever lived with a household member who smoked regularly. Exposure is not limited to spousal smoking, nor to any relative time-frame for duration of exposure. This broad definition of exposure possibly includes subjects who experienced little total exposure from ETS over the past 20 to 30 years. The high percentage of female controls exposed to ETS (84%) leaves a relatively small percentage of unexposed subjects.

KABA is one of the smaller studies in this report (24 cases and 25 controls, total). Exposure refers to current or past smoking of a spouse. SHIM, listed in Table 4-3 as a "probable O" found no association between risk of lung cancer and smoking by husbands, fathers, siblings, or coworkers. A high correlation was observed, however, with smoking by the father-in-law ($p < 0.005$), which the authors describe as plausible in the Japanese society (see Appendix A). The unpublished study by Varela (1987), denoted as VARE in this report, is quite large and warrants further attention. The author detects no effect from exposure to spousal smoking, but does find a significant increase in lung cancer incidence at a very high total exposure to ETS (spouse has smoked 150 person-years, in the author's terminology) (see Figure 3-4). Unfortunately, the pertinent data from this study are not included in the source for this report. Attempts to obtain these data from the authors have been, thus far, unsuccessful.

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TABLE 4-2. ADJUSTED RELATIVE RISKS AND POPULATION-ATTRIBUTABLE RISK OF INDIVIDUAL STUDIES (FEMALES)

Study	Percent controls exposed[1]	RR adjusted for misclass.[1,2] (RRM)	Excess RR from background[1,3] (RRB-RRM)	Population attributable risk[1,4]
AKIB	70	1.42(-,2.62)	0.2 (0,0.2)	33(0,57)
BROW	15	1.35(-,5.99)	0.2 (0,0.2)	20(0,49)
BUFF	84	- (-,1.83)	0 (0,0.2)	0(0,47)
CHAN	47	- (-,1.15)	0 (0,0.08)	0(0,13)
CORR	46	2.00(-,5.20)	0.2 (0,0.2)	40(0,68)
GAO	74	1.06(-,1.64)	0.03(0,0.2)	7(0,40)
GARF	61	1.19(-,1.91)	0.11(0,0.2)	18(0,43)
GENG	44	2.10(-,4.28)	0.2 (0,0.2)	41(0,62)
HUMB	56	2.31(-,6.61)	0.2 (0,0.2)	48(0,77)
KABA	60	- (-,2.45)	0 (0,0.2)	0(0,52)
KOO	49	1.44(-,2.67)	0.2 (0,0.2)	29(0,50)
LAMT	45	1.54(1,2.35)	0.2 (0,0.2)	31(0,45)
LAMW	44	2.01(-,3.71)	0.2 (0,0.2)	39(0,58)
LEE	68	- (-,2.56)	0 (0,0.2)	0(0,56)
PERS	43	1.13(0,2.09)	0.07(0,0.2)	6(0,40)
SVEN	66	1.14(-,2.81)	0.08(0,0.2)	15(0,58)
TRIC	43	2.07(1.03,3.81)	0.2 (0.02,0.2)	40(3,58)
WU	63	- (-,3.24)	0 (0,0.2)	0(0,62)
HIRA (Coh)	74	1.53(1.13,2.05)	0.2 (0.07,0.2)	37(14,49)
GILL (Coh)	72	- (-,4.91)	0 (0,0.2)	0(0,75)
GARF (Coh)	72	1.05(-,1.44)	0.03(-,0.2)	7(0,34)

[1] Values in parentheses are calculated from confidence bounds.

[2] Adjustments considered negligible for values of 2.5 or greater. Minus signs indicate a negative excess risk.

[3] Values truncated at 0.2, assumed to be a reasonable upper limit on excess risk for this exercise.

[4] See Appendix B.

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TABLE 4-3. POPULATION-ATTRIBUTABLE RISK BY STUDY (FEMALES)

Country	Study	Estimate	Confidence limit
Hong Kong	CHAN	0	13
U.S.	BUFF	0	47
U.S.	KABA	0	52
U.K.	LEE	0	56
U.S.	WU	0	62
Scot.	GILL(Coh)	0	75
Sweden	PERS	6	40
U.S.	GARF(Coh)	7	34
China	GAO	7	40
Sweden	SVEN	15	58
U.S.	GARF	18	43
U.S.	BROW	20	49
Hong Kong	KOO	29	50
Hong Kong	LAMT	31	45
Japan	AKIB	33	57
Japan	HIRA(Coh)	37	49
Hong Kong	LAMW	39	48
Greece	TRIC	40	58
U.S.	CORR	40	68
China	GENG	41	62
U.S.	HUMB	48	77
U.S.	VARE[1]	0	
Japan	SHIM[1]	0	
Japan	INOU[1]	70	

[1] Insufficient information to calculate. Estimate shown is a guess.

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Our remarks above pertain to studies that estimate zero-attributable risk. It is easier to depict study characteristics that reduce the likelihood of detecting an effect, than to speculate why a study may have concluded falsely that there is an effect. A false positive conclusion could result from an undetected causal variable that is correlated with ETS exposure. The likelihood of a false negative conclusion is enhanced if the sample size is small, or the study differentiates poorly between exposed and unexposed subjects.

The cohort study in Japan (HIRA) provides strong evidence of an increased lung cancer hazard associated with ETS exposure. Consideration of plausible confounding factors and covariables has not produced an alternative explanation, and implication of ETS as a causal factor is biologically plausible. The mixed results of epidemiologic studies in the U.S. may be partly due to statistical chance and study differences that affect the power to detect a lung cancer effect from exposure to ETS. There is also evidence to suggest that exposure differentials from spousal smoking may be larger in Japan, and possibly some other countries, than in the U.S. This would make a cancer-related effect more difficult to detect in the U.S. An estimate of U.S. PAR from evidence in Japan alone might lead to an overstatement. Prediction based on the overall summary has the advantages of using all the study data while mitigating but not ignoring the influence of the extreme outcomes.

4.5. SUMMARY AND CONCLUSIONS

The overall summary RR (before adjustments) for female NS obtained by the NRC (for 10 case-control and 3 cohort studies) is 1.32 (95% C.I. 1.16, 1.51). The corresponding value in this report (for 19 case-control and 3 cohort studies) is 1.41 (1.26, 1.57). The effect of nine additional case-control studies in the analysis of this report is to increase the RR from 1.3 to 1.4 and to reduce the width of the confidence interval. (Both changes increase the statistical significance.) The overall RRs for the 19 case-control studies by themselves, and for the three

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cohort studies by themselves, are nearly identical, even though the two types of epidemiologic studies have their own strengths, weaknesses, and potential sources of bias. The evidence from the U.S. studies, however, is weaker than for non-U.S. studies. The summary RR from raw data for seven U.S. case-control studies is 1.34 (95% C.I. 1.00, 1.79). For the 12 non-U.S. studies with raw data (all but two studies), the corresponding estimate is 1.45 (95% C.I. 1.24, 1.69). The overall summary RR for all U.S. studies (from seven case-control studies and one cohort study) is 1.25 (1.03, 1.52), which is statistically significant ($p = 0.025$ for a one-tailed test).

The overall RR for women NS is adjusted downward to 1.28 (95% C.I. 1.12, 1.45), using a modeling approach similar to that of NRC/Wald to estimate bias from smoker misclassification. Parameter values for the model were taken from recent sources. The adjusted estimate of RR is still statistically significant ($p < 0.01$). The parameter values also were varied over a plausible range (one at a time, but not jointly), leading to the conclusion that observed values of overall RR of up to 1.19 are consistent with a true RR of 1.0, i.e., could arise from misreporting bias alone. Although possibly substantial, misreporting bias is not sufficient to explain the entire excess risk associated with ETS exposure.

Based on these analyses and following the U.S. EPA guidelines for carcinogen risk assessment (Fed. Reg., 1986), EPA concludes that environmental tobacco smoke is a Group A (known human) carcinogen. This conclusion is based on a total weight of evidence, principally:

- Biological plausibility. ETS is taken up by the lungs and distributed throughout the body. The similarity of carcinogens identified in SS and MS along with the established causal relationship between lung cancer and smoking make it reasonable to suspect that ETS is also a lung carcinogen.
- Consistency of response. The two completed cohort studies and sixteen of the 21 case-control studies observed a higher risk of lung cancer among the female never-smokers classified as exposed to ETS. Evaluation of the total study evidence from several perspectives leads to the conclusion that the observed association between ETS exposure and increased lung cancer occurrence is not attributable to chance.

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- Upward trend in dose-response. Of the two major cohort studies, the Japanese study (Hirayama) demonstrates a strong association between passive smoking and lung cancer, including an upward trend in dose-response. The upward trend is well supported by the preponderance of evidence in the 13 case-control studies that classified data by exposure level. The Hirayama study has undergone extensive critical review that led to some corrections and revisions but failed to discredit the findings. Differences in life-style and culture may be a factor in the Japanese study reporting a stronger association between ETS and lung cancer than the American study (American Cancer Society).

- Detectable association at environmental exposure levels. Within the population of women who are lifelong nonsmokers, the excess lung cancer risk of those married to a smoker is large enough to be observed. Carcinogenic responses are usually detectable only in high exposure circumstances, such as occupational settings or in highly dosed experimental animals.

- Broad-based evidence. The 21 case-control and three prospective studies provide data from eight different countries and from a wide variety of study designs and protocols conducted by many different research teams. No alternative explanatory variables for the observed association between ETS and lung cancer have been indicated that would be broadly applicable across studies.

- Effects remain after adjustment for potential bias. Current and ex-smokers may be misreported as never-smokers, thus inflating the apparent cancer risk from ETS exposure. The evidence remains statistically conclusive, however, after adjustments for smoker misclassification. The summary estimate of relative risk from raw data of both the case-control and cohort studies is 1.41 (95% C.I. 1.26, 1.57) before adjustment for misclassification and 1.28 (95% C.I. 1.12, 1.45) afterward ($p < 0.01$).

To estimate the number of LCDs per year due to passive smoking, a further adjustment to RR is made to correct for background exposure to ETS, i.e., to make the estimate relative to zero ETS exposure. This additional adjustment leaves the overall RR estimate for female NS at 1.48 (1.21, 1.87). This same estimate is assumed for the relatively small number of male NS with a spouse who smokes. The available data on males suggests that the risk is at least as high as for females. It is assumed that 60% of the population of female NS of age 35 and over are exposed to ETS at levels equivalent to being married to a smoker, and that the remaining 40% are exposed to an average background exposure level (equivalently, average ETS exposure in the population of female NS is 60% of the way from the lower exposure level (from background ETS alone) toward the higher exposure level (from spousal smoking and background). It is

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estimated that about 27% (95% CI: 14%, 41%) of annual LCDs in never-smoking women are attributable to ETS exposure. Applied to the ACS's estimate of 6500 such cases in 1988, this percentage equates to 1750 (910, 2660) ETS-related LCDs in never-smoking women. The RR for male NS is likely at least as high as for female NS (NRC, 1986; Wells, 1988b). Applying the RR estimate for females to the ACS estimate of 3000 LCDs of male NS in 1988 gives an estimate of 810 males, making the total estimate 2560 for both sexes.

Compared to the wealth of epidemiologic data on never-smokers, particularly for women married to smokers, the information available for estimation of lung cancer risk in FS is not substantial. The absolute risk is higher in FS than in never-smokers, but the incremental risk from exposure to ETS is essentially unknown. For the purpose of including FS in the calculation of LCDs attributable to ETS, they are assumed to have the same relative risk from exposure to ETS as never-smokers. Based on this assumption and data regarding the number of former smokers in the U.S., the estimated annual number of LCDs due to ETS is 1260 (540 women and 720 men, as calculated in Appendix B). Inclusion of FS brings the estimated total number of LCDs per year from ETS to 3800. The component of this figure for married never-smoking females is based on the large quantity of epidemiologic data that is available. It has been statistically estimated with a 95% confidence interval included to indicate a range of statistical uncertainty. The component terms for unmarried women, for men, and for FS of both sexes are less well substantiated and subject to greater uncertainty.

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5. ENVIRONMENTAL TOBACCO SMOKE AND RESPIRATORY DISORDERS IN CHILDREN

5.1. INTRODUCTION

Medical, epidemiological, and experimental research of the past forty years has implicated smoking as a causal factor in an increasing array of diseases and detrimental health conditions. A recent workshop (Speizer, 1989) describes chronic obstructive pulmonary disease (COPD) as a heterogeneous group of disorders with the common element of obstructive airways disease. It concludes that over the last 25 years there has been a drastic and relatively sharp rise in COPD, particularly in men, and that much of the increase is associated with temporal trends in cigarette smoking. As knowledge unfolds an increasing breadth and severity of health effects related to smoking, the potential implications for passive smokers expand as well.

Unlike studies testing for a link between ETS and lung cancer, only a few studies have used adult subjects to test for respiratory symptoms. Infants and small children generally have been preferred because of better study control for exposure to ETS and confounding substances and because of the greater likelihood of an observable response due to their higher susceptibility. Children are more susceptible to respiratory disorders because their immunologic and respiratory systems are immature and pulmonary function is still developing (NRC, 1986; WHO, 1986). Also, "doses" of ETS are larger relative to their body size. Very young children experience prolonged exposure since they spend much of their time at home, and they are not exposed socially or occupationally to ETS or potential confounding agents. On the negative side, regular active smoking and experimentation become potential confounding factors in children at about age seven that may be understated by either parental or self-reporting. At early ages, particularly up to one or two years when study results of some health effects are most consistent, in utero exposure to products of tobacco smoke is another potential

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confounding variable. Finally, children are also relevant study subjects because of their population size. The number of American children less than five years old living in homes with at least one smoker probably exceeds nine million (American Academy of Pediatrics, 1986).

As observed in the report of the Canadian Pediatric Society (1986), the results of epidemiologic surveys on the potential effects of parents' smoking on their children were initially equivocal because it was often asked if either parent was a smoker. Only when the mother's and father's smoking habits were considered separately did it become evident that the mother's smoking habit was more important. It is not surprising that maternal smoking is more significant than paternal smoking in studies involving infants and young children. The predominant effect of maternal smoking, however, further complicates differentiating the influence of maternal smoking during pregnancy and during the postnatal period. A large study by Chen et al. (1988) has found increased respiratory illness in infants of nonsmoking mothers but with ETS exposure from other household smokers after birth. This somewhat discounts the role of the potential confounding effect of in utero exposure to tobacco products from the mother's smoking during pregnancy.

This chapter focuses on the evidence for an association of ETS exposure with chronic respiratory symptoms, acute lower respiratory illnesses, and impaired pulmonary function in children, with emphasis on epidemiologic studies that have appeared since the reports of the NRC and the U.S. SG in 1986. Studies on related topics are discussed in the last section, including the exacerbating effects of household ETS on asthmatic children and the potential association of parental smoking with the prevalence of additional respiratory disorders--asthma, upper-respiratory-tract infections, and middle ear effusion (an indicator of chronic middle ear disease).

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5.2. EXPOSURE OF CHILDREN

Biochemical data indicating *exposure* to ETS are predominantly assay results of cotinine concentrations in urine, saliva, or serum. Nearly all of the studies on adverse *health effects*, however, have relied on verbal reports of parental smoking or some other measure of exposure. Two exceptions have related health risks to cotinine concentrations. Strachan et al. (1989), who found a positive association between passive smoking and middle ear effusion in seven-year-old children, evaluated exposure to ETS by assaying salivary cotinine. The authors note that cotinine concentrations were related to the number of smokers in the household. Schwartz-Bickenbach et al. (1987) observed urinary cotinine concentrations in infants as a measure of exposure to nicotine and cotinine in breast milk and to nicotine in ETS. As noted by Jarvis (1989), the implicit assumption in utilizing cotinine concentrations as a measure of ETS exposure, i.e., as a dose-surrogate, to detect detrimental health effects that may be associated with exposure to ETS, is that cotinine concentrations are directly proportional to the uptake of risk-relevant compounds in ETS. Which compounds are risk-relevant to a particular detrimental health effect is generally unknown, however, and uptake may vary between individuals. Cotinine concentration appears to be the most promising internal measure of recent exposure to ETS. Studies that have addressed the validity or reliability of cotinine as an indicator of exposure to ETS are described next.

Jarvis et al. (1985) found saliva cotinine concentrations in nonsmoking schoolchildren to be related to smoking within the family. A clear increase in cotinine concentration was observed across the categories (1) neither parent smokes, (2) father only smokes, (3) mother only smokes, and (4) both parents smoke. Pattishall et al. (1985) measured serum cotinine in young children (6 to 12 years of age) and found a direct correlation with the number of smokers in the home, the amount smoked by the mother, and the amount smoked by others in the home. Coultas and colleagues (1987) surveyed salivary cotinine levels in children and adults. Similar to the study by

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Pattishall and colleagues, the major determinants of a detectable level of cotinine in children were the mother's smoking, father's smoking, and smoking of other household members. Henderson et al. (1987) found urinary cotinine to be a more sensitive indicator than serum cotinine among exposed children of day-care age. Both measures of cotinine, however, were significantly correlated with ETS exposure in the home as determined by levels of nicotine recovered from air samples and by the number of cigarette butts collected. Henderson et al. (1989) notes that urinary cotinine/creatinine ratios were remarkably stable in preschool children over a one-month period, and Jarvis et al. (1987) reports that cotinine measures were reasonably stable over one year in nonsmoking adolescent girls. The cotinine/creatinine levels of nine children (9 months to 3.5 years of age) exposed to 26.4 micro-grams/m^3 of nicotine from SS peaked at 4 hours and the elimination half-life was 29 hours (Goldstein et al., 1987). Greenberg et al. (1989) studied a representative sample of 433 healthy neonates in central North Carolina. Sixty-four percent lived in households with smokers or had contact with nonhousehold smokers. Urinary cotinine was found in 60% of all study infants. Seventy-five percent of smoking mothers smoked near their infants. The amount smoked in the infants' presence was the most significant correlate of cotinine concentration.

The cotinine studies clearly demonstrate uptake, metabolism, and systemic distribution of ETS in infants and implicate mothers' smoking as a principal source of exposure in their own children. There are indications of substantial host-related differences in cotinine concentrations among children, i.e., in experiments with controlled exposure to ETS, cotinine concentrations vary between individuals experiencing the same airborne concentration of ETS. Benowitz and Jacobs (1984) reported similar results for studies of cotinine in adults. To our knowledge, no researchers have estimated the component of variability due to inter-individual differences of absorption and metabolism in studies comparing cotinine levels with airborne concentrations of SS.

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5.3. RECENT EPIDEMIOLOGIC EVIDENCE

Studies that have appeared subsequent to the NRC and U.S. SG reports of 1986 are displayed in Table 5-1. They have largely taken potential biasing factors into account in the study design, protocol, or data analysis. It is often not feasible to measure and control for all the variables of potential interest, however, and it is difficult to do so perfectly when attempted. For example, active smokers among study subjects have generally been identified by self-reporting or parental reporting. Although there is no evidence to suggest that this method has been inadequate, the possibility of classification bias cannot be fully excluded. Other examples of variables to be considered include parental social class (Chen et al., 1988; Somerville et al., 1988; Willatt, 1986); heating and cooking fuels (Chen et al., 1988); parental illness that could either cross-infect their children or make the children genetically vulnerable (Chen et al., 1988; Willatt, 1986); and illnesses in the children that could mimic the effects of ETS (Chen et al., 1988; Geller-Bernstein et al., 1987). Typically these variables have been entered into a multiple regression or logistic regression model for statistical analysis or a method of stratification has been applied.

The epidemiologic studies emphasized in the U.S. SG and NRC reports on the health hazards of ETS to children between birth and adolescence are shown in Tables 5-2 to 5-4 for respiratory symptoms, respiratory illness, and pulmonary function. About 30 additional studies have appeared since the two major reports of 1986. Recent studies' characteristics are listed in Table 5-1, which includes a few entries for ailments in addition to respiratory symptoms, respiratory illness, and pulmonary function. Those last three categories, however, are the principal focus of this report and the topics of the next three sections. The general formats of the sections are similar: summary conclusions and issues from the NRC and U.S. SG reports are reviewed; selected recent studies are described that may bear on the weight of evidence and relevant issues; implications of the recent studies for the results and conclusions of the NRC and

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TABLE 5-1. EVIDENCE OF RESPIRATORY DISORDERS RELATED TO ETS EXPOSURE FROM SELECTED STUDIES SUBSEQUENT TO THE U.S. SG AND NRC REPORTS OF 1986.

Study	Age of subjects	Section reference	Reaction to ETS exposure
Chan et al., 1989	Children (7)	5.4.3 and 5.4.4	Wheeze in low-birth-weight cohort; cough in controls.
Charlton and Blair, 1989	Adol. (12-13)	5.4.1 and 5.7.5	Increased school absenteeism.
Chen et al., 1988	Infants	5.1, 5.3, 5.5.3, 5.5.4, and 5.7.3	Increased hospitalization.
Chen, 1989 (same sample data as entry above)	Infants	5.5.3 and 5.5.4	Synergism of passive smoking and artificial feeding on hospitalization.
Evans et al., 1987	Chil./adol. (4-17)	5.7.4	Increased emergency room visits; no increase in hospitalizations; no effect on pulmonary function.
Fleming et al., 1987	Infants/ chil. (0-5)	5.7.2	Increased upper respiratory tract infection.
Geller-Bernstein et al., 1987	Infants/ chil. (0-5)	5.3 and 5.7.3	Persistent wheezing in atopic children who were bottle fed.
Hinton, 1989	Infants/chil.	5.7.1	Higher chance of hospital admission for grommet insertion (middle ear).
Kallail et al., 1987	Children	5.7.1	No association with middle ear problems.

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TABLE 5-1. (continued)

Study	Age of subjects	Section reference	Reaction to ETS exposure
Kauffmann et al., 1989	Children (6-10)	5.4.4, 5.6.3, and 5.6.4	Maternal (but not paternal) smoking associated with decrease in FEV_1 and FEF_{25-75}, but not in FVC.
Lebowitz and Holberg, 1987	Chil./adol./ adult (5-25)	5.6.3 and 5.6.4	Long-term effect on children's pulmonary function.
Marks, 1988	Children (5)	5.4.3 and 5.4.4	More likely to cough or wheeze during physical exercise.
Martinez et al., 1988	Children (9)	5.7.3	Increased frequency of bronchial responsiveness and atopy in males but not females.
Masi et al., 1988	Adol./adults (15-35)	5.6.3 and 5.6.4	Exposure during lung growth period may affect males permanently.
McConnochie and Roghmann, 1986	Children (6-10)	5.4.3 and 5.4.4	Predicts wheezing only if family history is positive for respiratory allergy.
Murray and Morrison, 1989	Chil./adol. (1-17)	5.7.4	More severe asthma symptoms, especially in males.
Neuspiel et al., 1989	Inf./chil. (0-10)	5.4.3, 5.4.4, and 5.7.3	Increased incidence of post-infancy wheezy bronchitis.
Ogston et al., 1987	Infants	5.5.3 and 5.5.4	Increased incidence of alimentary and respiratory illnesses.

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TABLE 5-1. (continued)

Study	Age of subjects	Section reference	Reaction to ETS exposure
Ostro, 1989	Chil./adults (0-6)/(18-65)	5.7.5	Increased respiratory restricted days in adults, and bed disability days in young children.
Park and Kim, 1986	Children (0-14)	5.4.3 and 5.4.4	Dose-response relationship observed for cough, except with family history of cough or phlegm.
Reed and Lutz, 1988	Children	5.7.1	Dose-response relationship observed.
Somerville et al., 1988	Children (5-11)	5.3, 5.4.3, 5.4.4, 5.5.3, 5.5.4, and 5.7.3	Associated with wheeze, day and night cough, and bronchitis attacks. Asthma and morning cough increased, but not statistically significant.
Stern et al., 1987	Infants (0-2)	5.4.3, 5.4.4, 5.5.3, 5.5.4, 5.6.3, 5.6.4, and 5.7.3	Increased hospitalization for chest illness; cough, phlegm, and asthma more frequent.
Strachan et al., 1989	Children (7)	5.2, 5.4.4, and 5.7.1	Relation between salivary cotinine and middle ear effusion.
Teculescu et al., 1986	Adol. (10-16)	5.4.3, 5.6.3, and 5.7.2	More prevalent respiratory symptoms and upper airway infections; decreased forced expiratory flow. Effects more marked in males.
Willatt, 1986	Chil./adol. (2-15)	5.3 and 5.7.2	Associated with sore throats.

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U.S. SG reports are discussed. The recent evidence largely corroborates and strengthens the support for the similar conclusions of the two reports.

5.4. RESPIRATORY SYMPTOMS

The studies on respiratory symptoms cited in the 1986 reports of the U.S. SG and the NRC are listed in Table 5-2.

5.4.1. The U.S. Surgeon General's Report on Respiratory Symptoms

Children whose parents smoke were found to have a 30% to 80% excess prevalence of chronic cough or phlegm compared with children of nonsmoking parents. For wheezing, the increase in risk varied from none to over sixfold among the studies reviewed. The results of some of these studies may have been confounded by the child's own smoking habits (Colley et al., 1974; Bland et al., 1978; Kasuga et al., 1979). The association with parental smoking was not statistically significant for all symptoms in all studies (Lebowitz and Burrows, 1976; Schilling et al., 1977; Schenker et al., 1983). However, the majority of studies showed an increase in symptom prevalence with an increase in the number of smoking household members in the home.

Although misclassification of smoking children as nonsmokers must be considered, many studies showed a positive association between parental smoking and symptoms in children at ages before significant experimentation with cigarettes is prevalent. In addition, several studies (Bland et al., 1978; Weiss et al., 1980; Charlton, 1984; Schenker et al., 1983; Dodge, 1982; Burchfiel et al., 1986) found significant effects of parental smoking after adjusting for active smoking by the children. Acute respiratory symptoms represent an immediate health burden for the child. However, the long-term significance of chronic respiratory symptoms for the health of the child is unclear.

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